



Ensuring sustainable access to effective antibiotics for
EVERYONE - EVERYWHERE

HOW TO ADDRESS
THE GLOBAL CRISIS
IN ANTIBIOTIC RESEARCH
AND DEVELOPMENT

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Action on Antibiotic Resistance

Founded in 2005 as an international network, ReAct works to increase political awareness about antibiotic resistance, its drivers and its consequences to mobilize an adequate global response. ReAct's network is based on five continents, and its multidisciplinary team includes microbiologists, physicians, communication experts and policy specialists. Our vision is to see a world free from untreatable infections, and we believe that sustainable access to affordable and effective antibiotics is a core component of everyone's right to health.

ReAct and innovation

Since its creation, ReAct has been working on the issue of antibiotic research and development. In 2009, ReAct co-financed and developed in collaboration with the European Medicines Agency and the European Center for Disease Control, an analysis of the antibiotic pipeline, which for the first time documented the dearth in new antibiotics being developed. The same year under the auspices of the Swedish Presidency of the European Council, ReAct supported the organization of the first EU Member State conference called "Innovative incentives for effective antibacterials". Shortly after ReAct hosted the first big global conference for the broader AMR community on 'The Global Need for Effective Antibiotics'. Since then, ReAct has been engaged in numerous policy discussions and processes at national, EU and global levels, at the WHO and within the UN system. The inclusion of this principle the UN Political Declaration on AMR adopted by all Member States at the UN General Assembly in 2016 was therefore an important milestone.

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Foreword

I have worked numerous years as an infectious disease physician and witnessed the life-saving potential of antibiotics. Antibiotic resistance is a natural evolutionary phenomenon which cannot be stopped. While it can be slowed down through preventing infection, and optimizing the way current antibiotics are used, the world relies on a continuously refilled pipeline of new antibacterials to keep pace with resistance development.

Already when ReAct was founded in 2005, it was clear that the traditional market-based financing model for research and development of new antibiotics was failing. No new class of antibiotics had been discovered for almost two decades. The urgency of the issue made us include it as a core component of our work from the very beginning. I was worried back then, as I am now, that people alive today will experience in their lifetime how common bacterial infections become impossible to treat due to antibiotic resistance.

In 2009, ReAct supported the organization of the conference 'Innovative incentives for effective antibacterials' during the Swedish Presidency of the European Union and in 2010 we arranged an international conference on 'The Global Need for Effective Antibiotics'. Since then steps by individual governments, industry and the WHO have been taken trying to address this crisis. However, overall they either fall short of the scale of what is required, or do not sufficiently include or account for the needs of populations, healthcare systems, and governments in low- and middle-income countries.

This report argues that in order to get the solutions right, moving beyond the framing of antibiotic resistance as a medical challenge to one that reflects global inequality and lack of global solidarity, is required - with the ultimate goal of ensuring sustainable access to effective antibiotics for everyone, everywhere.

Today it is almost thirty-four years since the last class of antibiotics was discovered. The world cannot afford another 30 years of stalemate. New ways forward must be explored and seen as an opportunity to create a system that by design serves the health needs of us all - rich and poor. Access to effective life-saving antibiotics is a core component of everyone's right to health.

It is my hope that policy makers - with the deep global health inequality problems laid bare during the Covid-19 pandemic in mind - will be able to find the courage to truly do things differently going forward, and that this report can inspire to explore such new territory.



Professor Otto Cars
Founder ReAct



Executive summary

Effective antibiotics are a cornerstone of basic and specialized medicine. They are needed to treat everything from sepsis to pneumonia and to prevent infections in immunocompromised patients, such as those with HIV or cancer, and when performing surgeries and transplants.

Already, antibiotic resistance, including drug-resistant tuberculosis (TB), claims more than 750,000 lives every year, and lack of access to existing effective antibiotics contributes to millions of deaths annually. The emergence of bacterial resistance to antibiotics dismantles our ability to treat infections, alleviate human suffering, and save lives.

Seen from a global health perspective, resistant infections jeopardize the achievement of several Sustainable Development Goals (SDGs). Low- and Middle-Income Countries (LMICs) are more susceptible to the consequences of antibiotic resistance. These countries carry the highest burden of infectious diseases, lack access to novel and existing antibiotics to treat drug-resistant infections, often lack basic infrastructure such as water and sanitation, and have the least financial means to address drug-resistant infections.

Worldwide, overuse and misuse of antibiotics are major drivers of the development of bacterial resistance. For some infections, certain strains of bacteria have already become untreatable. To keep pace with global accelerating resistance, existing antibiotics must be kept effective by using them only when needed, while access to effective antibiotics must be expanded to everyone in need, and the antibiotic pipeline must be filled and continually replenished.

All classes of antibiotics currently on the market were discovered decades ago. This standstill in research and innovation can partly be explained by the complexity of the underlying science. Yet, the difficulty in developing new antibiotics has also been compounded by the withdrawal of many multinational pharmaceutical companies that over the years have redirected their focus to therapeutic areas providing greater economic returns. Interventions are clearly needed but governments have not yet responded with neither the scale nor the urgency required address this standstill.

This report outlines options for governments to construct a new model that delivers sustainable access to effective antibiotics. The report takes an “end-to-end” approach for the development and distribution of new antibiotics. This means a model that considers how the entire chain of actors, investments and regulatory measures, implicated in developing and bringing novel antibiotics to patients, should work to satisfy the following end goals:

1. **The right antibiotic is affordable and accessible to everyone in need**
2. **New and old antibiotics are managed in order to preserve their therapeutic effectiveness while minimizing the development and spread of resistance**
3. **Antibiotic production from a robust, reliable, and environmentally sound supply chain satisfies the global demand**

This report focuses upon five key challenges which governments should address and it provides suggested courses of action.

Challenge One: Setting research priorities that addresses the most significant and unmet global health needs

The latest clinical pipeline analysis by the WHO (2019) showed that out of the 60 candidates in clinical development, just 32 candidates target the WHO priority pathogens. However only two compounds target high priority multi-drug resistant bacteria. Moreover, pathogens prevalent in LMICs are under-prioritized.

The WHO has developed several tools to guide funders of antibiotic R&D more towards prioritizing the biggest unmet global health needs. These tools include the Priority Pathogens List from 2017 which lists the most urgent global priority pathogens to prioritize, four different target product profiles describing optimal and minimum required characteristics of end products, as well as frequent pipeline analyses.

However, R&D funders have not yet implemented a sufficiently coordinated approach to cover global priorities. R&D funding remains a largely national endeavor, shaped by national interests and priorities of funding countries. The result is a fragmented and uncoordinated global R&D landscape for antibiotics.

Recommendations:

- Establish a global coordination entity for early-stage R&D
- Establish a global system of Target Product Profiles to align research efforts with global needs

Challenge Two: Overcoming barriers in the early discovery and research phases

Considerable scientific challenges continue to complicate early discovery and research for new antibiotics. Promising compounds are harder to find as the low-hanging fruits in antibiotic discovery was picked in the period 1960-80. Lack of collaboration and sharing of research data is an impediment to overcoming these challenges, but the main challenge is lack of large-scale reliable funding. While it is sometimes argued that enough financing initiatives exist targeting early-stage research, scientific challenges for antibacterials remain largely unresolved. These include getting compounds into hard-to-permeate Gram-negative bacteria and understanding under what circumstances clinically relevant resistance mutations arise, to name a few.

The number of multinational companies with active anti-infective programs has fallen from 18 in 1999 to six in 2020. This means that almost all of the innovative research done to solve these challenges is now being done by smaller biotech companies and academia. These actors struggle crossing the so-called "valley of death" (moving a compound from basic to clinical research) because public funding is limited, and securing venture capital is almost impossible without an indication that larger companies will eventually acquire the compound. Many also do not have previous expertise in bringing a new antibiotics all the way to market. Efforts by the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Novo Repair Fund and the recently announced AMR Action Fund, primarily funded by pharmaceutical companies, may address parts of the problem.

However, ensuring that research targeting global priority pathogens is prioritized, and that appropriate access and stewardship policies are formulated and put in place for potential novel antibiotics, government funders should engage more actively and with clearer intent.

Recommendations:

- Increase public funding of basic, early-stage, and translational research
- Improve sharing of research data and compound libraries
- Improve existing structures that optimize early-stage research

Challenge Three: Financing late-stage clinical R&D without relying on price and sales revenues of the end-product

The traditional market-based model for financing development of medicines relies on companies recouping R&D investments through drug sales, i.e. by charging high prices and maximising sales in profitable markets before the patent protection period expires. This R&D model is not appropriate neither from the perspective of minimizing use, nor for ensuring affordable access. It is also not effective at incentivizing the development of antibiotics as evidenced by the decade long innovation void in antibiotics discovery.

Multinational pharmaceutical companies are often considered indispensable for testing and developing new antibiotics as they often claim that only they can manage and afford costly clinical trials. However, they consider the cost of these trials to be commercially confidential and high-end estimates usually generated by industry-funded experts, have been criticized as inflating the cost of clinical trials. This matter, because the size of these clinical trial costs influence both policy decisions and discussions about R&D incentives and pricing of end products. Yet, the riskiest part, and cumulatively, the largest driver of development costs for new antibiotics, are the pre-clinical phases, which tend to be paid for by or directly conducted in the public sector. Moreover, clinical trial costs vary, based on what is included in the cost calculation, and can be reduced depending on how they are done, and who conducts them.

In recent years, pharmaceutical companies and others have proposed additional market-based incentives from governments which are essentially extensions of the existing market-based model. However, after more than 30 years of evidence that the existing market-based R&D model is neither appropriate nor effective for developing antibiotics, it should be clear that more of the same will not be the answer. Instead, there is a clear need for increased public leadership to test new alternative models which aim to overcome challenges in an efficient and public health needs-driven way.

Recommendations:

- Increase transparency and reduce costs of clinical trials
- Separate (fully delink) the cost of research and development from the expectation of sales revenues (end-product price and sales volume)
- Introduce new incentives throughout clinical development
- Avoid "partial delinkage" as a means to pay for research and development of new antibiotics



Challenge Four: Ensuring sustainable production, quality, procurement, and registration of novel anti- biotics

Once a novel antibiotic has been brought through clinical development, a number of challenges in relation to production, registration, and supply of antibiotics need to be addressed.

Shortages of antibiotics are a chronic problem for many countries, which can lead to poorer treatment options for patients, and can be a driver of resistance. There are several supply-driven and demand-driven causes of antibiotic shortages. These include fragile, sometimes single source, global supply chains, fragmented demand forecasting, procurement challenges.

Antibiotic discharge from pharmaceutical production sites is a problem which is due to inadequate production and waste removal standards. Strengthening regulations and restricting the use of raw materials and active pharmaceutical ingredients (APIs) could reduce contamination, but interventions must avoid jeopardizing the availability or affordability of antibiotics.

Registration of new antibiotics in poorer countries is limited. For antibiotics introduced since 2014, registrations have been filed in fewer than five countries per year, slowing down approval and use. Even the registration of older off-patent products is limited, restricting availability in countries where there is a need. Such lack of access to appropriate antibiotics inhibits rational prescribing and use.

Poor quality antibiotics are also a serious problem. According to the WHO Global Surveillance and Monitoring System, antimicrobial drugs are the largest category of falsified and substandard medicines.

Antibiotic shortages, registration delays, and quality assurance, are transnational and global problems. These challenges could be addressed through a system of global rules-based governance, under the aegis of the WHO alone or with other relevant multilateral UN agencies. The WHO initiated the development of a global framework in 2015 – the Global Development and Stewardship Framework. However, progress has largely stalled due to political apathy from governments.



Recommendations (at global level):

- Restart negotiations of a global system of rules-based governance to:
 - Address imbalances between supply and demand
 - Ensure controlled production and supply
 - Promote environmentally appropriate antibiotic production
 - Facilitate timely registration

The absence of a global governance framework should not discourage governments from acting. An incremental approach at national/regional level to improve sustainable access, registration, and manufacturing of antibiotics should however create a pathway to eventually conclude a global framework.

Recommendations for interim national or regional action:

- Adopt national legislation that sets antibiotic production standards
- Collaborate on setting procurement rules and/or guidelines that encourage environmentally appropriate production
- Require patent pooling as a condition on public funding
- Establish public or non-profit production capacity

Challenge Five: Ensuring sustainable access to new antibiotics in countries

Introducing new antibiotics into health systems in countries without propagating historical mistakes of overuse and misuse of antibiotics, and widespread lack of access, is a major challenge. Inappropriate use of existing antibiotics is widespread in almost every country. The OECD estimates that 50% of antibiotic use in High-Income Countries (HICs) is unnecessary. They therefore have an urgent moral responsibility to curb their significant excess use. In LMICs, where health systems are often weak and under-financed, curbing overuse and misuse of antibiotics is also a clear priority, but such efforts must be carefully crafted to avoid exacerbating the lack of access to essential medicines, including effective antibiotics. Simultaneously expanding access to antibiotics, while also restricting access to avoid misuse and overuse of antibiotics, is a truly unique challenge in global health.

Current worldwide (mis)management of antibiotics and the unwillingness so far of pharmaceutical companies to eliminate misaligned incentives, such as sales-based bonuses, is testament that individual pharmaceutical companies should not be in charge of developing future policies to ensure appropriate access to, and stewardship of, new antibiotics. Misaligned incentives to oversell antibiotics and current affordability and availability barriers in countries can to a large degree be addressed through rules-based global governance as described in challenge 4.

National governments are ultimately those responsible and accountable for the introduction and distribution of new antibiotics in a manner that guarantees safe and responsible use, ensures equitable affordable access, and minimizes the emergence of resistance development. This will require increased top-down efforts through government action, but equally important will be the support of a bottom-up approach involving civil society actors much more systematically.

Recommendations:

- Strengthen healthcare systems globally and provide financing options for LMICs
- Support civil society efforts to develop human resource capacity and structures
- Establish a global WHO task for the introduction of novel antibiotics.

Abbreviations

- ACT-A** – The Access to COVID-19 Tools Accelerator
- AMA** – African Medicines Agency
- AMR** – Antimicrobial resistance
- API** – Active pharmaceutical ingredients
- BARDA** – The U.S. Biomedical Advanced Research and Development Authority
- BPG** – Benzathine penicillin G
- CARB-X** – Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
- CEWG** – The Consultative Expert Working Group on R&D Financing and Coordination
- CHAI** – The Clinton Health Access Initiative
- COVAX** – COVID-19 Vaccines Global Access Facility
- CRP** – The WHO's Collaboration Registration Procedure
- CRE** – Carbapenem-resistant Enterobacterales
- DDDs** – Defined Daily Doses
- EDCTP** – The European Developing Countries Clinical Trials Partnership
- EMA** – The European medicines Agency
- FDA** – The U.S. Food and Drug Administration
- GARDP** – The Global Antibiotic Research and Development Partnership
- GDF** – The Global Drug Facility for Tuberculosis
- GLG** – The One Health Global Leaders Group
- GMP** – Good Manufacturing Practices
- HERA** – The EU Health Emergency Preparedness and Response Authority
- HICs** – High-Income Countries
- HTA** – Health Technology Assessment
- IMI** – The Innovative Medicines Initiative
- IP** – Intellectual Property
- JPIAMR** – The Joint Programming Initiative on AMR
- LMICs** – Low- and middle-income countries
- MER** – Market Entry Reward
- MPP** – The Medicines Patent Pool
- ND4BB** – New Drugs for Bad Bugs program
- OECD** – The Organization for Economic Co-operation and Development
- PQ** – The WHO Prequalification Program
- PPC** – Preferred Product Characteristics
- PPL** – The WHO Priority Pathogens List
- R&D** – Research and Development
- SDGs** – The Sustainable Development Goals
- SMEs** – Small and Medium Enterprises
- STRAMA** – The Strategic Group for Rational Antibiotic Use and Reduced Antibiotic Resistance
- TB** – Tuberculosis
- TLV** – The Swedish Dental and Pharmaceutical Benefits Agency
- TPP** – Target Product Profile
- UTIs** – Urinary Tract Infections
- WHO** – The World Health Organization

Introduction.

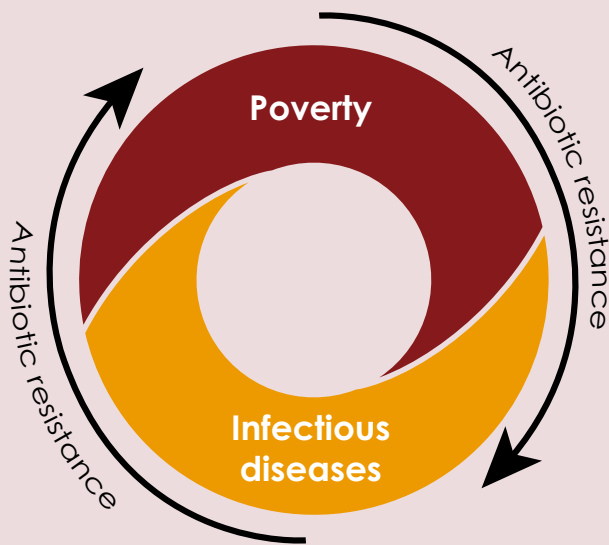
Effective antibiotics are a cornerstone of basic and specialized medicine. The emergence of bacterial resistance to antibiotics is slowly dismantling our ability to treat infections, alleviate human suffering, and save lives. The COVID-19 pandemic is a clear reminder of the deadly consequences when treatments and vaccines do not exist, or are not available to the people who need them.

Consequences of Antibiotic Resistance

A future without effective antibiotics would have a devastating impact on global public health, jeopardize the achievement of several Sustainable Development Goals (SDGs),¹ and have enormous economic consequences.² A century of significant progress within global public health is at serious risk of being reversed.

Without effective antibiotics, basic and community health care, and specialized health care (such as cancer treatments, surgery, transplants, complicated deliveries, and care of preterm babies) will be significantly more difficult and sometimes impossible. Antibiotic resistance, including

drug-resistant tuberculosis (TB), already claims more than 750,000 lives every year, and lack of access to existing effective antibiotics contributes to millions of deaths annually. Populations in LMICs are bearing the brunt of this public health crisis^{3,4} given that these countries carry the highest burden of infectious diseases, lack access to novel and existing antibiotics to treat drug-resistant infections, and lack basic infrastructure such as clean water and access to sanitation. Drug-resistant bacteria cause 40–60% of infections in Brazil, Indonesia, and Russia compared to an average of 17% in OECD countries.⁵ In some LMICs, resistance rates reach 80–90% for certain antibiotic/bacterium combinations.⁶ A lack of access to antibiotics causes the death of at least six million people annually, including one million children who die of preventable sepsis and pneumonia.⁷ One-third of the world's population do not have access to sanitary toilet facilities, more than 660 million people do not have access to clean drinking water, and one in every eight people currently defecates in the open.⁸ These factors all exacerbate the emergence and spread of resistant bacteria.



People living in poverty are more prone to infectious diseases

Circumstances of poverty increase the spread of antibiotic resistance

The cost of having an infectious disease drives people into poverty

Antibiotic resistance significantly increases cost of treatment driving people into poverty or making treatment inaccessible

Figure 1. The vicious cycle. People living in poverty are not only more vulnerable to antibiotic resistance, but are also less able to prevent or treat antibiotic-resistant infections.

People living in poverty are also often unable to prevent or respond to drug-resistant infections, and poverty can leave people with little choice other than to engage in practices that drive antibiotic resistance, such as irrational use and self-medication. With poverty on the rise again due to the economic fall-out of the COVID-19 pandemic,⁹ the lack of access to effective antibiotics will remain one of the most pressing challenges and a cause of avoidable morbidity and mortality.

As with climate change, antibiotic resistance and the development of effective solutions must be framed, not just as a medical challenge but as a crisis that reflects global inequality and a lack of global solidarity, which can only be solved through global cooperation.

Antibiotic innovation

Worldwide over- and misuse of effective antibiotics are major drivers of resistance. For some infections, certain strains have now become untreatable.¹⁰ To keep pace with accelerating resistance, existing antibiotics must be kept effective, access to effective antibiotics must be expanded to everyone in need, and the antibiotic pipeline must be filled and continually replenished.

The standstill in antibiotics innovation can partly be explained by the difficult underlying science. Yet, the complexity in identifying new antibiotics has been multiplied by the withdrawal of both investment and the loss of human

resources in the antibacterial field by the pharmaceutical industry. The withdrawal of research-intensive, multinational pharmaceutical companies was both a foreseeable and deleterious outcome of these companies' continued dependence on the blockbuster business model (with annual profit expectations at the billion dollar level). This level of profit expectation in the "regular" pharmaceutical market, discourages multinational pharmaceutical companies from investing in antibiotic development, since profits in this field generally (with a few exceptions such as daptomycin¹¹) are more modest.

Over the last decade, political interest from governments in addressing the exit of large pharmaceutical companies has not been commensurate with the scale and urgency of the growing problem. This may be because addressing this problem will require long-term engagement and large-scale investments by governments. Discussions have so far mostly been concerned with finding ways to re-enlist the big multinational pharmaceutical companies, within the constraints of preserving their traditional business model and have largely been fruitless.

The time has come for governments to start viewing their public investments as an opportunity to establish a sustainable system designed to serve the global health needs of both rich and poor. This system should be built around a set of smaller actors with more compatible business models to develop, produce, and distribute affordable antibiotics.

Starting with the end goals

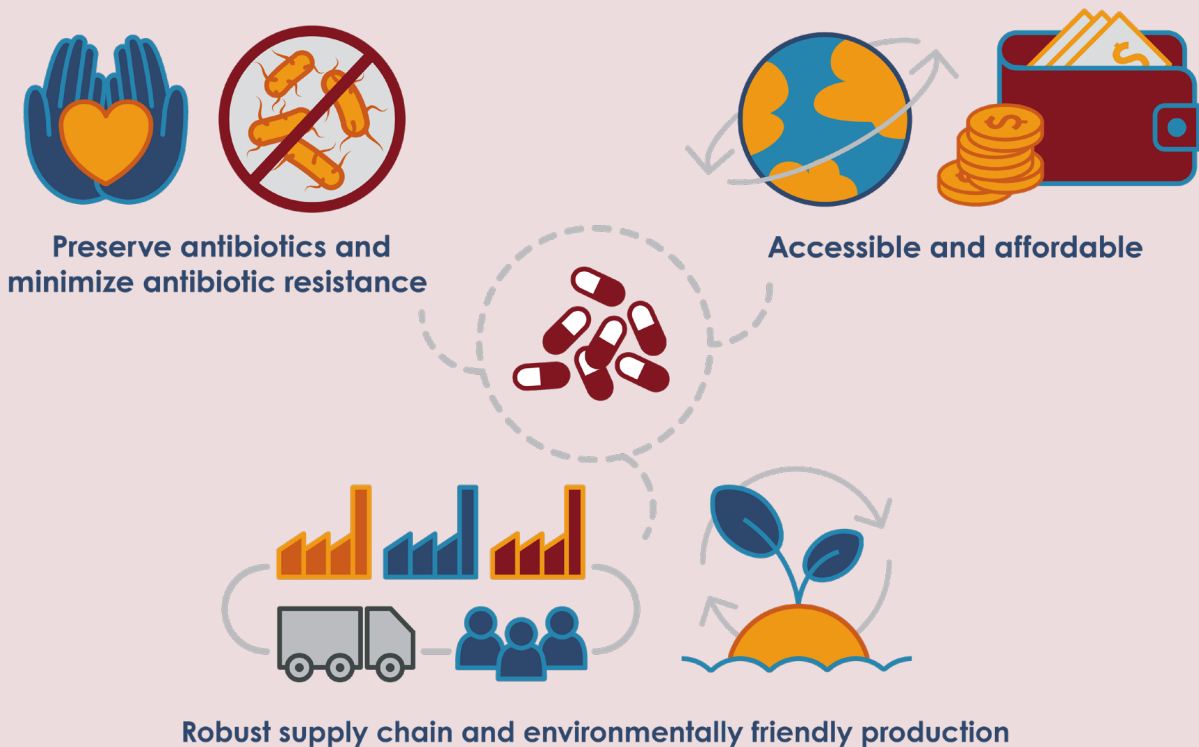
ReAct supports an “end-to-end” approach for the development and distribution of new antibiotics. This means a model that considers how the entire chain of actors, investments and regulatory measures implicated in developing and bringing novel antibiotics to patients, should work to satisfy the following end goals:

- The right antibiotic is affordable and accessible for everyone in need.
- New and old antibiotics are managed to preserve their therapeutic effectiveness while minimizing the development and spread of resistance.
- Antibiotic production from a robust, reliable, and environmentally sound supply chain satisfies the global demand.

Delivering on these three goals should result in global “sustainable access” to antibiotics that are available and affordable, produced appropriately and at adequate levels, and managed for maximum therapeutic effectiveness, while minimizing the development and spread of resistance throughout the supply chain.

This report outlines options to construct an alternative model by taking an end-to-end approach. It identifies the key challenges in achieving these end goals and present recommendations for consideration. It is our hope that this report can contribute toward envisioning a more just and equitable approach for the development, stewardship, and access to antibiotics that leaves no one behind.

Sustainable access to antibiotics



Addressing the key challenges.

Often, the global discussions on how to fix the antibiotic pipeline have only focused on solving the economic part of the failing development model. Recent bankruptcies of smaller companies and the withdrawal of large pharmaceutical companies from the antibiotic R&D field have led to a narrative that the innovation crisis can be solved by reversing that trend i.e., transforming antibiotic R&D into a commercially attractive pursuit for (big) pharmaceutical companies.

Yet the lack of profitability for pharmaceutical companies is just one of many reasons why the existing model is not appropriate for antibiotics: research priorities are skewed by the pull of profitable markets; unresolved scientific challenges complicate the early stages of research; financial difficulties in crossing the so-called “valley of death” and conducting clinical R&D; polluting production, fragile supply systems and lacking registration of new antibiotics; and, finally, the challenge of introducing a new antibiotic into health systems, without replicating past practices of overuse, misuse and widespread lack of access to antibiotics.

This report identifies five key challenges that need to be addressed by governments:

- 1) Setting research priorities that addresses the most significant and unmet global health needs
- 2) Overcoming barriers in the early discovery and research phases
- 3) Financing late-stage clinical R&D without relying on price and sales revenues of the end-product
- 4) Ensuring sustainable production, quality, procurement, and registration of novel antibiotics
- 5) Ensuring sustainable access to new antibiotics in countries

Challenge One

Setting research priorities that addresses the most significant and unmet global health needs

Understanding the problem

Funding of R&D is today mostly seen as a national (and in the case of the EU, regional) endeavor, shaped by national interests, needs, and priorities. With R&D funding primarily coming from just a few HICs, the specific health needs of poorer countries are often overlooked.

To address this problem of “He who pays the piper calls the tune”, several tools have been developed to help steer financing for antibiotic R&D more towards the biggest global health needs. In 2017 the WHO developed the Priority Pathogens List (PPL) which lists three categories of priority pathogens to target research efforts towards according to their urgency: critical, high, and medium priority.¹² In total, 12 families of bacteria are included.

The WHO has also produced quantitative and qualitative analyses of both the pre-clinical and clinical pipelines to take stock of progress. The first preclinical pipeline analysis showed a small trend of more pathogen-specific approaches being applied – presumably a result of the development of the PPL.¹³ However, the most recent clinical pipeline analysis from 2019 showed that, of the 60 candidates in clinical development, just 32 target the WHO priority pathogens and the majority only confer limited benefits over existing treatments. Moreover, only two compounds target the three multi-drug resistant Gram-negative bacteria considered a “Critical priority”¹⁴ which are spreading at alarming speed and urgently require novel treatment options.

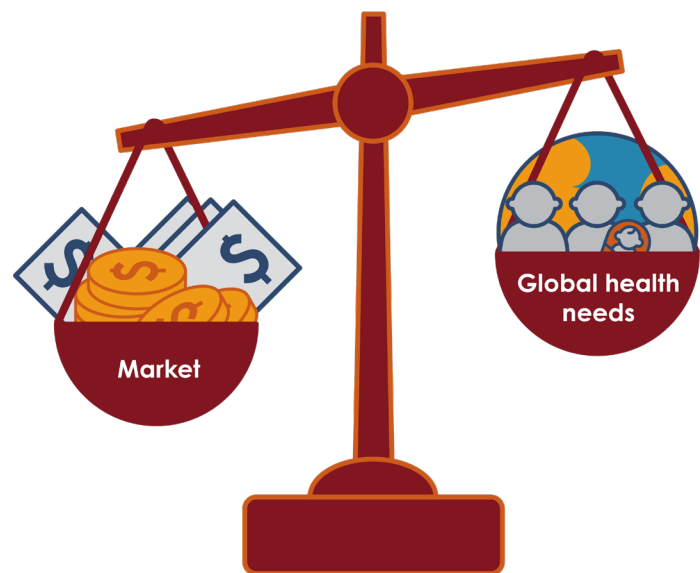
Finally, the WHO has recently compiled and published Target Product Profiles (TPPs), or Preferred Product Characteristics (PPCs) as they call them, for four novel antibiotics, addressing enteric fever, gonorrhea, neonatal sepsis, and urinary tract infections.¹⁵ TPPs and PPCs are methods used by both the private sector and product development partnerships to outline desired end-product specificities. As such, they provide a direction of travel for the entire R&D process and typically set out a product's optimal and minimum required characteristics as well as a description of the intended use, target populations, and desired attributes of a potential new product. A TPP can (and should) also include a price target to encourage low-cost production throughout the development process.

While robust guidance tools exist to support prioritization of R&D financing for antibiotics, governments have not yet

engaged in more systematic voluntary coordination with other R&D funders. The result is a fragmented R&D landscape, which, as the WHO's pipeline analyses shows, is not able to respond to the global rise of antibiotic resistance globally.

In 2018 the German G20 Presidency created the global AMR R&D Hub. There was some initial hope that it could help improve R&D prioritization and coordination. However, the Hub, created through the G20 rather than the multilateral WHO, lacked the broad-based support – especially from LMICs – to assume a global mandate from the beginning and has also not sought to take on such a role. To date, the Hub has instead produced a “Dynamic Dashboard” which provides an overview of global funding streams for AMR R&D; a global “Incentives Overview”; and an overview of the clinical pipeline. Currently a number of prospective market analyses for compounds in the later stage of clinical development are also being conducted.¹⁶

Profitable markets skew global research prioritization



Box 1. Needs of HICs skew global research prioritization – the example of *Clostridioides difficile* (*C. diff*)

▶▶▶ The pipeline for the Gram-positive pathogen *C. diff* is an example of how responding to the needs of the most profitable markets is more attractive for developers.

- *C. diff* causes serious infections, mostly in hospitalized patients who have received multiple courses of antibiotics. These infections are predominantly a health threat in HICs, and in fact, *C. diff* was not included on the WHO's list of global priority pathogens. This is because these infections should primarily be managed through prevention, control, and stewardship measures; and because existing treatment options are still available.
- *C. diff* is however a serious problem in the U.S., with an estimated 500,000 cases every year. The U.S. Center for Disease Control (CDC), therefore, lists *C. diff* as a "critically important" pathogen. The pipeline for *C. diff* is one of the most well-stocked pipelines in the antibiotic field.^{16a}

▶▶▶ By contrast, for some priority pathogens that have a serious health impact in LMICs, such as *Salmonella typhi* and *A. baumannii*, there are hardly any promising drug candidates in the pipeline.

While all R&D to combat drug-resistant infections is welcome, increased governmental funding efforts and coordination are required to better address the global priorities and the health needs of lower income countries.



Recommendations.

1. Establishing a global coordination entity for early-stage R&D

Increased efforts to address clear research gaps on the PPL is urgently needed. Inter governmental alignment and coordination on research prioritization could be done voluntarily but requires a far more systematic approach than what is the case today. Aside from using the WHO's pipeline analyses, the Global AMR R&D Hub's Dynamic Dashboard could support such voluntary coordination, as it collects data on financing streams and provides an updated overview of the current pipeline and of existing incentives.¹⁷

However, given the urgency of the issue, it would likely be far more effective to confer a mandate upon an existing or a newly created inter-governmental body to coordinate global R&D and, preferably, to finance early-stage antibiotic research. This could be achieved either by governments expanding the mandate of an existing body, such as the WHO R&D Observatory, which is already collecting data, monitoring, and analyzing the R&D needs of developing countries to support coordination of global health R&D. Alternatively, a new global research coordination body focused on antibiotic R&D could be established, as has been proposed several times by a number of actors and academics.^{18,19,20,21} Such an entity could be hosted either by the WHO alone or in collaboration with other relevant UN organizations.

Replenishing the antibiotic pipeline will not be achieved through a one-time funding initiative but must be an ongoing effort in order to ensure continuous new alternatives, as resistance develops to drugs in use. The financing required for a new global R&D coordinating entity to effectively finance early-stage research would therefore need to be predictable, sufficient, and long-term. Stable financing options, such as levies and solidarity taxes, should be considered. One successful example is Unitaid's financing model, which is based on an airline ticket tax collected from 29 countries,²² including both traditional donor countries and LMICs.²³ Norway contributes to Unitaid through a carbon tax.

Replenishing the antibiotic pipeline requires long-term, predictable, and sufficient funding.

2. Establish a global system of Target Product Profiles to align research efforts with global needs

Establishing a global system of TPPs can be a helpful tool to coordinate and steer R&D funding for antibiotics and to achieve certain pre-defined desired attributes, which makes them more suitable for being used in resource scarce contexts.

The use of TPPs is already standard practice in a number of non-profit product development partnerships, such as the Global Antibiotic Research and Development Partnership (GARDP),²⁴ The Drugs for Neglected Diseases Initiative,²⁵ the Medicines for Malaria Venture,²⁶ and for the development of the MenAfriVac²⁷ (a vaccine against meningitis A for African countries). They provide good examples of how setting out a price target in the TPP has in fact resulted in the successful development of affordable and appropriate end-products.

Current WHO efforts to assemble and develop TPPs for new antibiotics described above, should be supported by the WHO Member States and expanded into a comprehensive global system (as was also recommended by the Boston Consulting Group in their report on antibiotic incentives to the German G20 Presidency in 2017²⁸).

Going forward the process to development of TPPs should meaningfully involve end users, i.e., patients, doctors, and nurses in different settings and regions. The process should apply practices included within the Good Participatory Practice (GPP) guidelines, which are intended to ensure respectful community engagement and trust through collaborative partnerships. These guidelines have been developed to foster engagement with communities for the development and testing of HIV and TB technologies,²⁹ and, more recently, were adapted for use during the COVID-19 pandemic.³⁰ Their core principles of transparency and participation are equally relevant for research, development, and testing related to antibiotic resistance.

Challenge Two

Overcoming barriers in the early discovery and research phases

Understanding the problem

There are considerable scientific challenges in early discovery and research for new antibiotics.³¹ Promising compounds are harder to find, as the low-hanging fruits in antibiotic discovery were picked between the 1960s and the 1980s.

This crisis is not new. Throughout the 1990s and early 2000s, pharmaceutical companies placed emphasis on the “genomics approach” and “rational” drug development, with a focus on target genes and high throughput screenings, which proved unsuccessful. Large-scale efforts by GSK and others yielded leads at a frequency four- to five-fold lower than in other therapeutic areas and did result in any novel antibiotics reaching the market.³² As a result all classes of antibiotics on the market today were discovered decades ago³³ and the few antibiotics that have been brought to market since the 1980’s are modifications of existing products, more likely to be affected by already existing resistance mechanisms. Even when applying the most optimistic scenario, new treatment options will likely only be available in a decade, according to the WHO.³⁴ The world is currently burning through a scarce and finite resource.

In recent years, the pre-clinical pipeline has been strengthened somewhat and is considered more innovative and diverse than the clinical pipeline.³⁵ This is in part due to funding efforts such as the U.S. based Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)³⁶ and the Novo Repair Impact Fund, the EU-funded New Drugs for Bad Bugs program (ND4BB), the Joint Programming Initiative on AMR (JPIAMR), and the U.S. Biomedical Advanced Research and Development Authority (BARDA). However, how many of the molecules found in the pre-clinical pipeline that will make it to the patients, is yet unknown. Due to the high failure rate of these early stage high-risk projects, the preclinical pipeline is still not considered sufficiently robust despite the relative improvement.³⁷

Historically, it is estimated that more traditional antibacterial drugs have a ten-fold lower yield in the discovery stage of identifying promising new compounds when compared to all other drug classes. Many of the scientific challenges leading to these higher failure rates, such as penetration issues, efflux, and managing toxicity, remain unresolved and will still affect any traditional antibiotic compounds in the pre-clinical pipeline today.³⁸

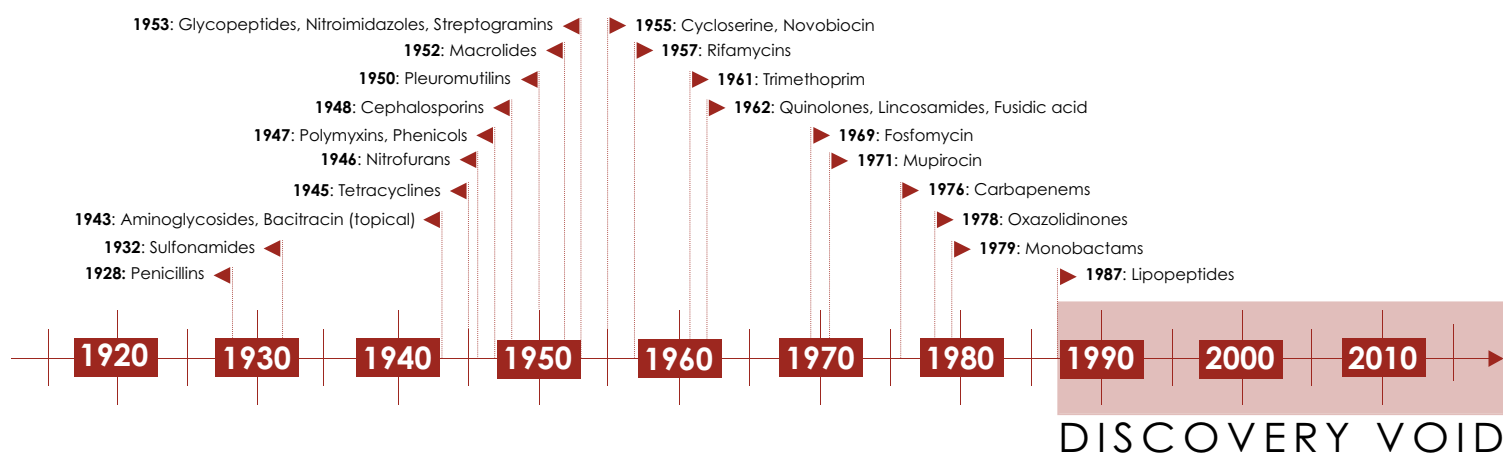


Figure 2. Time-line of the discovery of different antibiotic classes in clinical use. “The discovery void” refers to the period from 1987 until today, as the last antibiotic class that has been successfully introduced as treatment was discovered in 1987.

These scientific difficulties have been compounded by several other factors. Lack of collaborative approaches and data sharing can impede progress and cause wasteful duplication of research efforts.³⁹ The global R&D response to the COVID-19 pandemic is a clear reminder that significant global coordination of biomedical R&D, including priority setting, clinical trials, and financing, is needed to avoid siloed efforts and to ensure that research efforts yield the desired outcomes.⁴⁰

Moreover, most multinational pharmaceutical companies have exited the antibiotics field. In 2011, Pfizer shut down its primary antibiotic research center and relocated the research facility to Shanghai,⁴¹ which at the time was regarded as a “crushing blow”⁴² to the field of anti-infectives research. Since then, a number of big companies have followed suit. Between 2016 and 2018, four big companies – AstraZeneca, Sanofi, Novartis (including its subsidiary, the Medicines Company), and Allergan – all exited from antibiotic R&D. Merck’s 2014 buyout of longstanding anti-infectives company Cubist, widely touted as a sign of big pharma re-entry, was followed by the layoff of 120 researchers and the closure of Cubist’s early-stage discovery research unit just three months later.⁴³ The launch of the AMR Action Fund in 2020 by a group of 20 pharmaceutical

companies, which aims to invest 1 billion USD over 10 years in promising compounds, introduces new financial (and technical) resources to the field, but neither reverses nor repairs the multi-decade decline in investments by the largest pharmaceutical companies.

Over the last two decades, the number of multinational companies with active anti-infective programs has fallen from 18 to just six⁴⁴ in 2020. Instead, numerous biotech companies, which are smaller and focused on developing only a few compounds mostly with public support, have filled the gap in the early stages of clinical development (see figure 3 below). The Pew Trust estimates that 70% of the small companies involved have no previous experience with bringing a product to the market.⁴⁵

A few smaller companies, such as Achaogen and Melinta Pharmaceuticals, have in recent years succeeded in shepherding early-stage discoveries through clinical development and brought new antibiotics to market. Yet both companies failed to earn sufficient revenues to sustain their businesses. Over a twelve-month period in 2019 and 2020, both companies filed for bankruptcy as the near-term revenues for each company’s new antibiotics were too limited in the United States (see Box 2 for details on Achaogen).

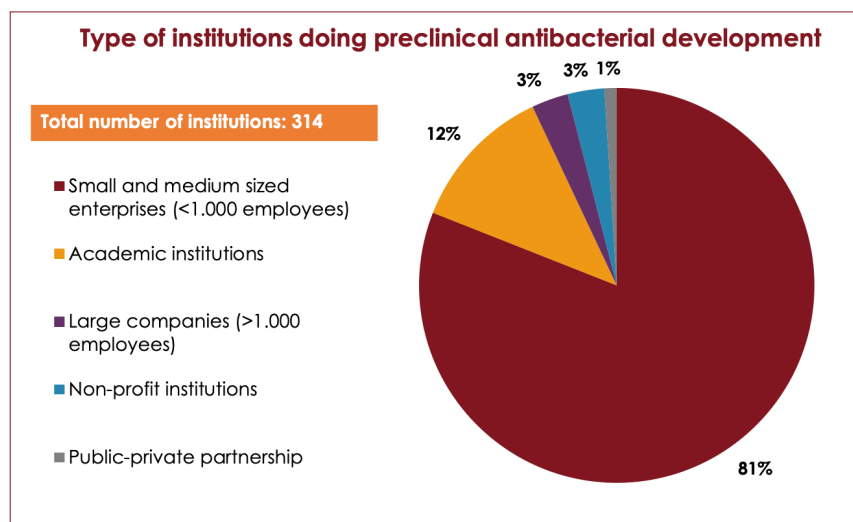


Figure 3. SMEs and academia dominate the preclinical research space accounting for 93% of the actors involved.

Adapted from Theuretzbacher U. et al. 2020. The global preclinical antibacterial pipeline. *Nat Rev Microbiol*, 18:275-285. <https://doi.org/10.1038/s41579-019-0288-0>

Box 2. The case of Plazomicin

The commercial pull of the U.S. market, which represents roughly half of the global pharmaceutical market,⁴⁶ means that companies often file for registration first in the United States. However, the bankruptcy of the company Achaogen in 2019, which only registered its flagship product, the antibiotic Plazomicin, in the United States, illustrates how such a strategy can fail.

Achaogen received a “priority review designation” from the U.S. Food and Drug Administration (FDA) for the antibiotic Plazomicin, which is a modified compound from an already existing class of antibiotics – aminoglycosides. This meant that the drug was put at the front of the line for review by the FDA and was subsequently approved in 2018 for treating urinary tract infections (UTIs) caused by drug-resistant bacteria in patients with no alternative treatment options. The FDA, however, did not approve a second indication – treating resistant bloodstream infections caused by *Carbapenem-resistant Enterobacteriales (CRE)*⁴⁷ – for which Achaogen had also sought market approval, as not enough patients had been enrolled in a trial for that indication.

Plazomicin was included relatively quickly in the WHO’s Essential Medicines List within the so-called “Reserve” category of last line antibiotics to treat certain multidrug-resistant infections – a testament to the need for the drug globally. However, Achaogen only registered and made the drug available commercially in the United States.

After regulatory approval, Plazomicin did not sell as much in the U.S. as expected (likely due to the limited approval for use in treating resistant UTIs, where other treatment options were already available). Analysts had projected peak sales worth around 500 million USD for Plazomicin.⁴⁸ However, six months after it was launched, sales revenues were less than one million USD.⁴⁹ This was insufficient to sustain Achaogen’s operations, and the company filed for bankruptcy in 2019, only one year after the FDA’s approval of Plazomicin.

During Achaogen’s bankruptcy, Plazomicin was acquired by the Indian pharmaceutical company, Cipla, which applied for market approval at the European Medicines Agency (EMA). Cipla subsequently withdrew the application, as the product was considered commercially and financially unviable, given the costs of generating the necessary approval and post-approval data required for an EMA market authorization.⁵⁰

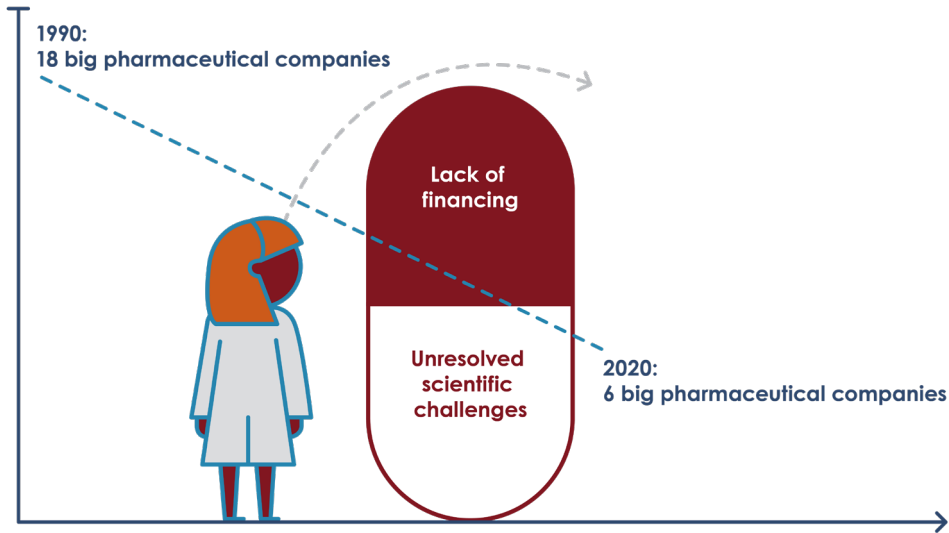
Achaogen’s bankruptcy and Cipla’s decision to withdraw its application at the EMA serves as an important reminder that the market actually works, in the sense that ‘me-too’ drugs with limited clinical benefits over existing treatments (which Plazomicin was for UTIs in the U.S.) provide smaller financial returns. As such, Achaogen’s bankruptcy is not necessarily a good example of a broken market for antibiotics, nor should the company’s collapse serve as a justification to pressure governments to establish large-scale pull incentives for the multinational pharmaceutical industry.



The example of Achaogen’s bankruptcy points however to a number of other factors that companies and governments should consider when constructing a viable antibiotics market. These include:

- To get truly novel classes of antibiotics, incentives and subsidies targeted to encourage the development of these need to be a priority.
- Follow-on innovation or repurposing of existing classes of antibiotics that meet a particular urgent need (e.g., overcoming a particular resistance mechanism, or development of a specific formulation, or reducing side effects) can and should also be supported – though on a smaller scale.
- Supporting and investing in innovation in the design of clinical trials and patient recruitment is needed. This includes enlisting more LMICs in trials to generate data for treatment of more complicated resistant infections and data that go beyond the initial market approval requirements, for example, additional evidence to guide the clinical use of the drug.
- Creating a global registration system where countries with the largest health needs are prioritized.

The scientists' challenges in antibiotic research



Basic research, discovery, and early-stage research are almost entirely funded by the public and the philanthropic sector⁵¹ and carried out by academic researchers and small biotech companies. The typical business model for these actors is to develop compounds up to the early clinical stages and then sell these compounds to a larger company. For this reason, these smaller companies and academic groups often lack expertise in conducting the later stages of development, market registration, production, and distribution.

Even if smaller companies or academic groups wanted to expand into the clinical phases of development, crossing the so-called "valley of death" (moving a compound from basic to clinical research) difficult because public funding for such translational research is limited, and securing venture capital is almost impossible unless there is an indication that a larger company will eventually acquire the compound. As an alternative, some biotech companies have in recent years chosen to partner with the not-for-profit product development partnership – the Global Antibiotic Research and Development Partnership (GARDP) – for the later stages of drug development.⁵²

The recently announced AMR Action Fund,⁵³ which is funded and sponsored mostly by 20 large pharmaceutical companies (see additional discussion on the Fund in Box 3), may partly help alleviate the current poor financial outlook facing smaller companies. By injecting 1 billion USD of investment over ten years to support late-stage clinical development, the Fund may make it easier for these smaller companies to secure funding and investment to bring compounds into clinical development.

While financial contributions from the private sector are welcome, governmental engagement and investments is important in all phases to be able to steer investment priorities better and define and ensure that appropriate access and stewardship policies are put in place. Put differently, governments should start viewing its public investments as an opportunity to establish a sustainable R&D system for antibiotics, which by design and intent, serves the global health needs of both rich and poor.

Recommendations.

1. Increased public funding of, and engagement in, basic, early-stage, and translational research

Overcoming the scientific challenges in early-stage discovery and research largely depends on the availability of significantly increased financial resources. While public and philanthropic investments to support the early stages of research and development of anti-bacterial compounds have increased over the last 10 years, more governments should introduce funding or expand their existing investments to support basic, early-stage, and translational research. Such funding should be tied closely to the PPL, and ideally be channeled into a global R&D coordination entity (as recommended under Challenge 1).

The [UK Review on AMR](#) made initial recommendations as far back as 2015, stating that a 2 billion USD early-stage innovation fund should be established to “cover the blind spots left by the current level and structure of grant funding.”⁵⁴ The Boston Consulting Group, in a report commissioned by the German Government, issued a similar recommendation shortly thereafter for the creation of a fund with an annual budget of 200 million USD over 10 years.⁵⁵ Since then, about 1/3 of that has been mobilized (CARB-X in the U.S., and the Novo Repair Impact Fund, being the only new money added to the field with 480 million USD⁵⁶ and 165 million USD, respectively⁵⁷).

2. Improve sharing of data and sharing of compound libraries

Even as governments invest more resources to support early-stage R&D, such contributions should be used to transform the R&D ecosystem to become more collaborative, transparent, and coordinated. This could be achieved by attaching conditions to funding, which require researchers to commit to improved openness and data sharing that goes beyond sharing information and data merely through the publication of results in open access scientific journals.

[Easily accessible data](#) from ongoing global antibiotic research would enable researchers to learn from others' mistakes, avoid wasteful duplication of efforts, and likely optimize the discovery process. Smaller initiatives towards this end have been established,⁵⁸ but a more comprehensive and intentional approach would be beneficial.

[Open access compound](#) libraries would help identify promising compounds in the public or private sector, which other entities could take forward, and which would encourage greater collaboration amongst disparate entities in developing new antibiotics.⁵⁹

Governments should leverage increased public funding to transform the R&D ecosystem to become more collaborative, more transparent, and more coordinated.

3. Improve existing structures that optimize early-stage research

There have been some attempts to try to optimize early-stage R&D. Below we discuss two of them, their respective advantages and disadvantages, and how they could be improved to better serve public health needs.

The EU-funded project ENABLE is effectively a virtual drug discovery platform.⁶⁰ The research projects included get support from academic and industry experts reviewing their early-stage data at several "stop or go" decision points, to either approve continued financial support, or reject projects for compounds which are not sufficiently promising.

In six years, ENABLE has advanced 24 compounds from 110 expressions of interest and it is an example of how deliberate oversight, data sharing, and review by scientific bodies can improve the productivity of early-stage R&D funding. This core structure and the expertise that has been developed, with its potential for linking portfolios and strategies of different initiatives, is something to learn from and improve on. It is important to note that the European public-private "Innovative Medicines Initiative (IMI)", of which ENABLE is a part, has been criticized over the years for being far too industry dominated and not sufficiently defending public interest⁶¹. This comes as no surprise, as an aim of the IMI is to improve the competitiveness of the European-Based Pharmaceutical industry.⁶² Going forward and building on any existing initiative needs to include placing antibacterial research in a context that has the aim to improve public health.

Established in 2016, CARB-X is a R&D funder that provides grants for projects in the early stages of research – or from the hit-to-lead to phase I.⁶³ While the financial contribution of CARB-X to antibiotic R&D has been positive, its scope and budget is still far from sufficient to reinvigorate the pipeline at the scale needed.

Interestingly, receiving CARB-X funding comes with several obligations required of grant recipients. First, CARB-X requires that grant recipients develop and publish an 'access and stewardship plan'.⁶⁴ Second, CARB-X requires that emerging end-products be manufactured, marketed, and sold according to certain principles (the Wellcome Trust's equitable access principles⁶⁵ and the commitments set out in the Pharmaceutical Industry's Declaration on AMR⁶⁶). Third, as a part of the terms and conditions for contracts signed between CARB-X and its recipients, the Wellcome Trust has a right to apply "march-in rights" if its equitable access principles have not been satisfied.

While CARB-X should be commended for introducing such obligations, there are a number of improvements that should be implemented to ensure that its early-stage grants are leveraged so that antibiotics are in fact affordable and that access to them is sustainable.

First, CARB-X should not apply the same principles as those set out by the pharmaceutical companies (as enumerated in the pharmaceutical industry's Declaration on AMR), since these same companies have a self-interest in introducing few obligations that govern its policies and practices. Instead, CARB-X should adopt the government defined principles as stated in the UNGA Political Declaration on AMR⁶⁷ and other adopted WHO norms and standards.^{68,69} Additionally, while CARB-X should mandate the use of march-in rights where companies fail to meet access-related requirements, such an exercise of rights should not be held by a private philanthropy such as the Wellcome Trust that is neither accountable nor fully transparent to the public.

Instead, the following approaches for CARB-X should be considered:

- Concrete minimum requirements that ensure affordable pricing for all countries (for example tied to target prices set out in TPPs developed by the WHO).
- Require registration of new products widely and quickly and to use appropriate international facilities – such as the WHO Prequalification Program and Collaborative Registration (see Challenge 4).
- Encourage or require companies to manage intellectual property, including through licensing to the Medicines Patent Pool, in order to facilitate affordability, supply security, and sustainable access.
- Make requirements incorporated in "access and stewardship plans" legally enforceable.

Challenge Three

Financing late-stage clinical R&D without relying on price and sales revenues of the end-product

Understanding the problem

The market-based model for financing development of pharmaceuticals relies on companies recouping their R&D costs through sales of the end-product, i.e. charging high prices and maximizing sales before the patent protection period runs out.⁷⁰ However, this traditional incentive model has not been successful in bringing forward novel antibiotics for decades.

Multinational pharmaceutical companies, which have capital and other resources on hand, are often considered indispensable for testing and developing new antibiotics. For example, in January 2020, the Wellcome Trust argued that “Clinical trials...require resources, infrastructure and expertise that can only be provided by large pharmaceutical companies”.⁷¹

Big pharmaceutical companies often claim that costly clinical trials justify high prices for the end product, but consider the data concerning the cost of clinical trials to be commercially confidential. Consequently, R&D costs are shrouded in secrecy. High-end estimates cited by pharmaceutical companies, usually generated by industry-funded experts, have been criticized as inflating the cost of clinical trials^{72,73} (and thus “padding” the overall cost of R&D).⁷⁴ This matters, because the size of these clinical trial costs influence both policy decisions and discussions about R&D incentives and pricing of end products.

The cost of clinical trials depends on how the costs of clinical trials are calculated, how clinical trials are designed, and who conducts them. One reason why industry-generated trial costs appear high is that such estimates tend to include cost of capital, or the cost of lost opportunity from other investments for which capital could have been deployed.

The opportunity cost of capital has a significant impact on the assumed cost of clinical trials. In a report to the Public Health Agency of Sweden, the Swedish Dental and Pharmaceutical Benefits Agency (TLV) compared three different cost-studies⁷⁵ – namely, Baraldi (2018), Sertkaya et al. (2014), and DiMasi (2016). Figure 4 shows the wide variance

between these estimates (ranging from less than 1 billion to 2.5 billion USD) and that roughly half of the estimated costs in all three studies are due to the calculated opportunity cost of capital. The report notes that even if governments also need to account for the cost of capital, the costs associated with this are likely to be far lower for governments than for companies⁷⁶. Similar figures and conclusions about the cost of capital in pharmaceutical R&D in general have also been reported by others.^{77,78}

A financial model developed jointly by the WHO and European Investment Bank to model the cost, and risk, of antibiotic development estimated that the full end-to-end cost of developing one new antibiotic is 162.9 million USD, with an expenditure of 122.4 million USD for post launch commercialization and additional studies.⁸⁰

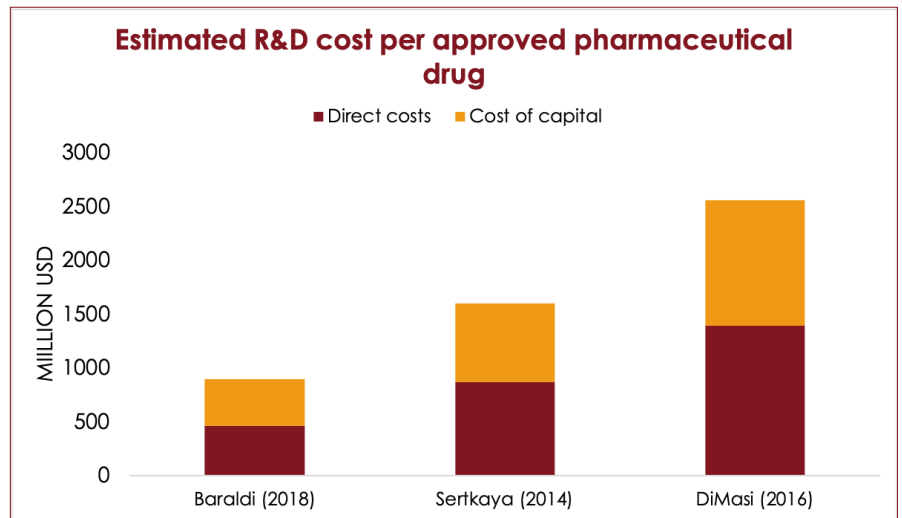


Figure 4. Three study estimates of drugs developments costs with breakdown of direct costs and costs of capital (indirect costs). Note only Baraldi et al. and Sertkaya et al. focus specifically on antibiotics. DiMasi focus on all drug types.⁷⁹

Furthermore, the riskiest, and cumulatively the largest driver of development costs for new antibiotics, is the pre-clinical phases. Figure 5 shows the costs associated with the various clinical phases. In the three studies referenced above, the pre-clinical phases incur the highest costs when considering the total bill associated with bringing one new compound

to market. This is likely due to the high number of projects that fail in the early stages. This is of relevance since the public foots almost the entire bill for these riskier early-stage phases. Conventionally, late-stage trials are cited as the most expensive part of the drug development process, which is true if the costs of only one individual drug are considered. These later stage trials, however, are far less risky.

A key challenge and cost driver of late-stage clinical development of new antibiotics is the difficulty in recruiting suitable trial participants.⁸¹ Bacterial infections progress rapidly; therefore, potential trial participants need to be enrolled quickly into a trial, often before a precise diagnosis can confirm the suitability of the patients. Since these patients, for safety reasons, cannot be moved between hospitals if infected with multidrug-resistant pathogens, many hospitals and doctors, sufficiently trained in the trial protocol, need to be recruited and involved. Some proposals on how to improve patient recruitment and the clinical trial infrastructure have been made already,⁸² but more innovation in this area is needed.

Phase III trials are large studies of the investigational drug's efficacy in larger patient groups (often involving between 1,000 and 3,000 patients). However, proposals have been made to change and streamline the standards for drug approval at regulatory agencies, such as the FDA⁸³ and the EMA, with the aim of reducing clinical trial requirements for obtaining market authorization for new antibiotics.⁸⁴ Regulators are also accepting well-performed pharmacokinetic and pharmacodynamic (PK/PD) studies to replace certain clinical studies.⁸⁵ Thus, investments in post-market surveillance networks and phase IV trials for novel antibiotics become even more important and necessary to assure safety.

Lowering the standards of what is known about a novel drug's safety and efficacy requires rigorous pharmacovigilance following market approval to capture serious and rare side effects. Furthermore, when regulatory agencies grant early approval, more responsibility for assuring the safety and efficacy is placed on governments and health

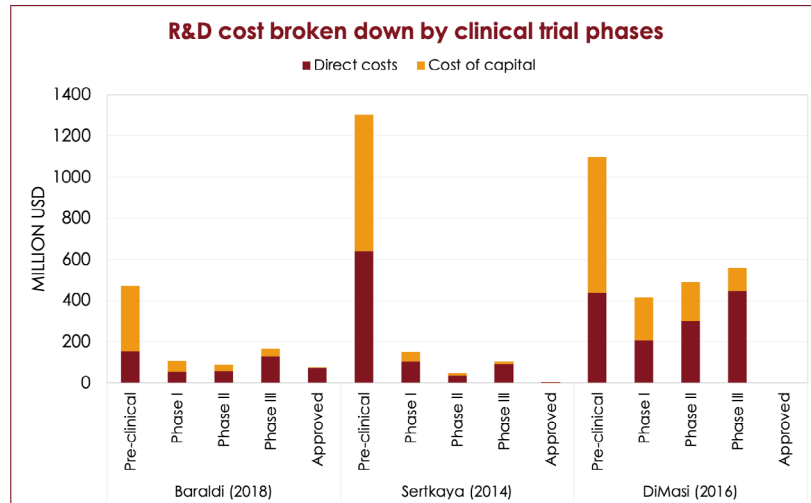


Figure 5. In all three studies the preclinical phase is accumulatively the most expensive. .⁷⁹

systems. Even when companies are asked to conduct additional post-market studies, there is no guarantee that such studies will be completed. A study found that five to six years following approval, only half of the post-market studies required by the FDA of drug companies had been completed and one-fifth had not been initiated.⁸⁶

Finally, even if reduced trial size and regulatory requirements could make R&D less expensive, it may in fact not improve a company's commercial prospects and financial viability, if these reduced requirements lead to a situation where data to justify and guide clinical use of the antibiotic is lacking. Above all, patient safety must remain the top priority for guiding the development of future regulatory pathways for antibiotics and, once a drug is registered, resources must be prioritized for pharmacovigilance.

►►► **Box 3. The AMR Action Fund**

►►► In July 2020, 20 pharmaceutical companies, with the backing of the International Federation of Pharmaceutical Manufacturers Association and based on previous work carried out by the WHO and the European Investment Bank, launched the AMR Action Fund. To compensate for the lack of public funding, as well as the lack of venture capital, the Fund will pool capital from participating companies to act as an investor in selected antibiotic projects in stages II and III of clinical development. In February 2021 the European Investment Bank, the Wellcome Trust and the Ingelheim Boehringer Foundation announced that they are contributing €20 million, £50 Million and 50 Million USD respectively to the Fund.

While the 1,1 billion USD is a welcome addition to the field, it is far from enough of what is needed to address the many gaps that have emerged after decades of funding neglect. The Fund should not be viewed by governments as a substitute or alternative to their own further engagement for a number of reasons:

- First, despite the contribution from the European Investment Bank, public oversight over the funding decisions and policy development is limited, since the Fund will be governed only by companies, with limited possibility for government contributions and influence.
- Secondly, given that the Fund operates as a profit-driven investment entity there is a risk that selected projects, even with the advice of its Independent Scientific Advisory Board, might predominantly focus on projects which have commercial potential in HIC markets. While the Fund presumably cannot fund projects that its Independent Scientific Advisory Board rejects, it is also under no obligation to fund all projects which are approved by the Scientific Advisory Board. Unless an alternative public funding pathway is established, the AMR Action Fund, will therefore as the primary funder for late-stage antibiotic R&D, de facto have the decision power over which compounds are brought to market, and which ones aren't. The Fund will also have significant control of the shaping (or not) of access and stewardship policies for the antibiotics it chooses to fund. This matter because such decisions profoundly influence countries' ability to address antibiotic resistance effectively.
- Finally, the investing drug companies, having had very limited involvement – if any at all – in the discovery of these products, may be able to secure the rights to these products as they are about to come to market, for example, through acquisition or licensing agreements. This raises issues around conflict of interest, unless the Fund specifically prohibits investing companies from privileged rights to acquire or in-license such investigational compounds.

In recent years, pharmaceutical companies and others have tried (mostly unsuccessfully) to secure additional market-based incentives from governments which are essentially extensions of the existing market-based model.

These proposals include:

- Patent term extensions (extending the patent term of a medicine beyond twenty years so that companies can charge monopoly prices for a longer period of time).
- Premium pricing strategies (increasing the cost of the medicine, for example, by claiming that a higher price reflects its “value”).
- Transferable market exclusivity (in exchange for developing a new antibiotic, a company is allowed to extend a monopoly on a different medicine that can or is earning blockbuster revenues. De facto, this means pushing the costs on to other patients).
- Data exclusivity extensions (providing companies with extra years of exclusive right over clinical trial data, which prevents a drug regulatory authority from referring to an originator’s clinical trial data to approve a generic competitor).⁸⁷
- Market Entry Rewards (MERs) (a substantial innovation prize given at the point of market entry. It has been suggested that MERs should be worth 1-4billion USD per antibiotic⁸⁸ on top of maintaining all ownership over IP to be a compelling incentive for multinational pharmaceutical companies and their investors).

However, after 30 years of evidence that the existing market-based R&D model is neither appropriate nor effective for developing antibiotics, it should be clear that more of the same will not be the answer. Instead, we clearly need increased public leadership, and to test new alternative models which aim to overcome challenges in an efficient and public health needs-driven way.

Minor modifications of the traditional market-based R&D model for pharmaceuticals, that further entrench this model, will not solve the antibiotics R&D crisis. Governments cannot keep doing the same and expect a different outcome.

Recommendations.

1. Increase transparency and reduce costs of clinical trials

In a more publicly steered model, requiring increased transparency of pharmaceutical R&D costs should be a clear priority for governments to allow more informed discussions about incentives. Moreover, different ways to optimize and reduce costs of clinical trials should be considered by looking at who could carry out the trials. Clinical trials in other research areas have been shown to be significantly cheaper when either carried out by not-for-profit organizations, such as the Drugs for Neglected Diseases Initiative,⁸⁹ or by the public sector, where the clinical research can be embedded within public health care facilities. Drug development models embedded within public health care facilities can ensure that research is more strongly associated with the clinical application of the medicine, which is to provide clinical care. For example, this has been a guiding philosophy of the Mario Negri Institute, which has viewed the divide between research and clinical practice as “the greatest risk in clinical medicine,” and, as such, has sought to ensure that research on treatments is “nested within practice.”⁹⁰ The Public Health Agency of Sweden has carried out a range of clinical trials within public hospitals on older drugs to improve dosing, change treatment length, and to assess potentially useful drug combinations, and recruited subjects from the normal patient cohort in these hospitals, with significantly lower associated costs.⁹¹

Another way to reduce costs associated with recruiting patients is through the use, and global extension of existing, publicly subsidized clinical trial networks. An expert group convened by the Wellcome Trust found that late-stage clinical trial costs for new antibiotics could be reduced by as much as 23–60%, depending on how such networks were set up, and would likely also expedite clinical development.⁹² The Wellcome Trust also recently launched a Request for Proposal to establish a pilot and potentially a Secretariat for a Global Clinical Trials Network to support Phase III trials, follow-on, and optimization of new antibiotics.⁹³

The location of global clinical trial networks could also help solve some challenges with patient recruitment by enabling trials to take place in countries where there is a known prevalence of a particular resistant pathogen (instead of situating the trial in industrialized countries). Global clinical trials involving a broad spectrum of countries, such as the recent WHO-run Solidarity Trial⁹⁶ for several COVID-19 treatments, are avenues for further exploration. While multi-country trials can be important for reducing costs and assuring the safety and effectiveness of new antibiotics in diverse populations, it is of course important to ensure that these do not result in developers avoiding regulatory safeguards or ignore requirements for ethics reviews and local acceptance of clinical trials.

Box 4. Examples of existing clinical trial networks

- COMBACTE-NET in Europe⁹⁴
- The MERINO group in Australia⁹⁵
- The Penta Child Health Research Network⁹⁶
- The Anti-bacterial Resistance Leadership Group (ARLG) in the United States⁹⁷

Several of these networks have received substantial public funding, which should hopefully have helped to bring down trial costs. The European Union has a program designed to fund such networks in LMICs, known as the European Developing Countries Clinical Trials Partnership (EDCTP).

2. Separate (fully delink) the cost of research and development from the expectation of sales revenues (end-product price and sales volume)

A different, sustainable, and long-term funded model, driven by governments, is needed for antibiotics. This should allow governments and public entities with a public health mandate to develop policies to achieve low prices and appropriate sales levels. The concept of “delinkage” has been widely acknowledged for its potential to ensure affordable access without excess use of antibiotics.⁹⁹ Delinkage was originally developed as a practical model to overcome the lack of R&D for neglected diseases, which primarily affect people in low-income countries and are not regarded as commercially relevant for drug companies (see more in box 5).

ReAct has played a critical role in adapting the principle of delinkage to the field of antibiotic research and development,¹⁰⁰ whereby the cost of R&D is separated from high prices and sales volumes. This makes the model for antibiotics different from both the conventional market-based pharmaceutical innovation model, which relies on maximizing sales of high-priced drugs in key high-income markets, and the generic pharmaceutical business model, which is based on low price/high volume sales. The stewardship component – or the need to limit antibiotic sales to preserve their effectiveness – makes adapting the concept of delinkage to the antibiotics field more complex than applying it to other types of medicines, where the aim is only to lower medicine prices.

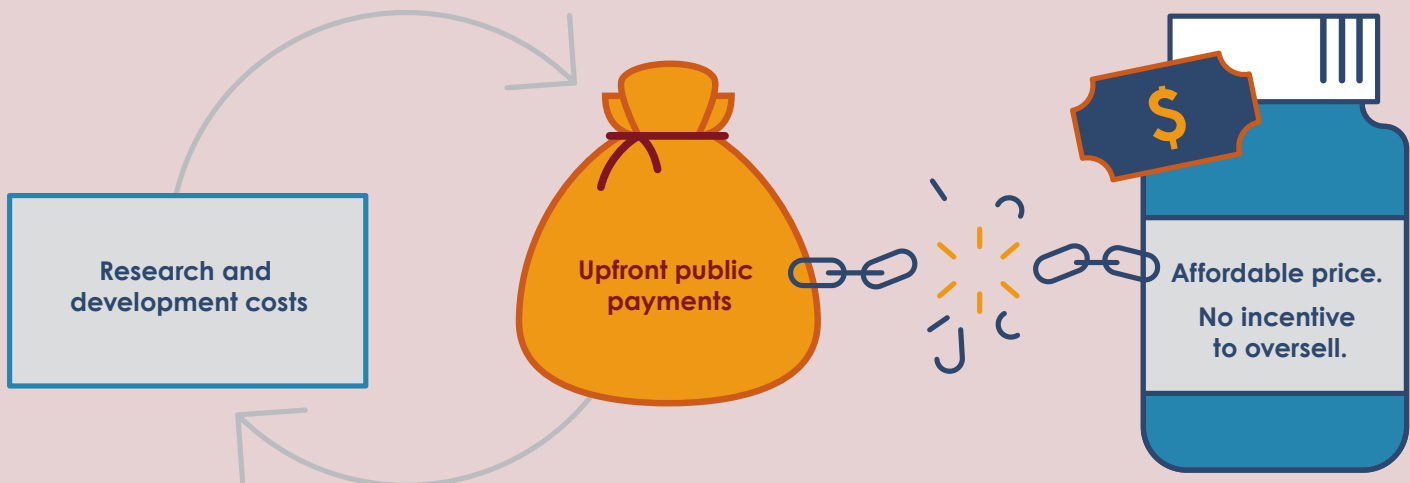
Delinkage builds on the simple idea that governments, instead of paying for antibiotic R&D once the drug is brought to market, should shift to paying upfront throughout the R&D phases. Compensating companies for their R&D investments upfront breaks the link between product sales and recouping R&D investments.

The current market-driven pharmaceutical R&D model



The costs of research and development lead to companies charging high prices and maximizing sales of the medicine during the patent protection period. These sales profits are then in theory used to invest in new research and development.

A delinked pharmaceutical R&D model



Paying companies for their R&D investments upfront, means these investments do not need to be recouped through sales profits. Low-cost production and public health driven distribution models can therefore be established from the day the drug receives market authorization.

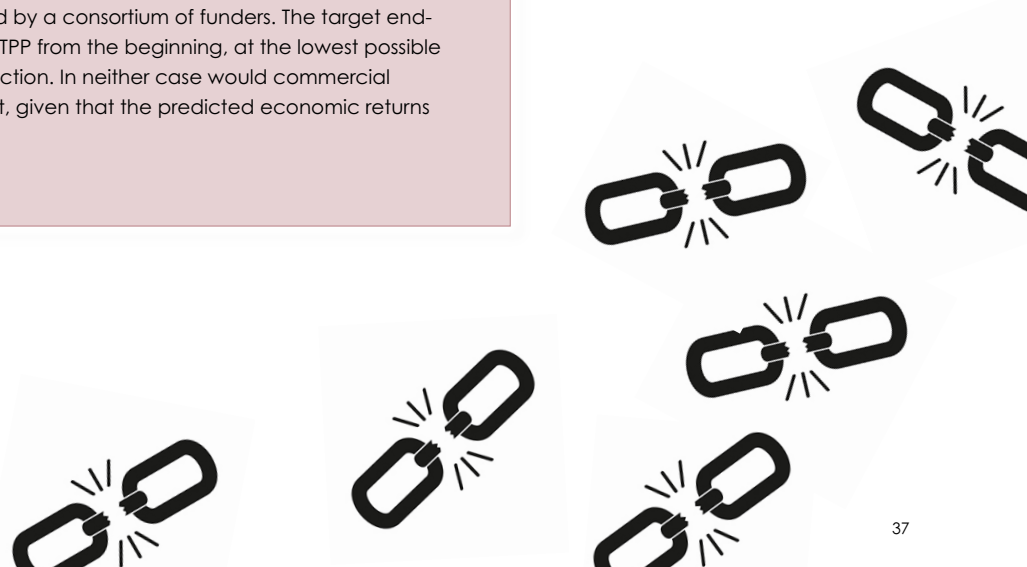
Box 5: Delinkage

The term “delinkage” appeared in the WHO’s 2012 report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) entitled, “Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination”¹⁰¹ which specifically sought to assess the viability of new approaches to finance biomedical R&D. The report noted:

“Delinkage is a powerful principle. The intellectual property system encourages a business model that allows developers of products to recoup the costs of R&D and to make profits through charging consumers on the basis of the exclusivity conferred by intellectual property rights. Depending on the pricing policies of the originator in developing countries, this can result in the patient, or those purchasing on behalf of a patient such as a government or a health insurer, being unable to afford a life-saving treatment. Delinking, which can happen in a number of different ways, is a means of divorcing the funding of R&D from product pricing. Once a patent has expired, delinking occurs naturally because generic competition should bring the price down to levels determined by market conditions and the cost of production rather than by R&D cost.”

Delinkage has already been implemented successfully in practice, although such examples are currently found outside the field of antibiotic development. Two well-known, early examples of delinkage in practice were: the development of new medicines by the Drugs for Neglected Diseases Initiative, including a patent-free novel antimalarial combination therapy (ASAQ)¹⁰², and the development of the vaccine against Meningitis A by the product development consortium MenAfriVac¹⁰³. From the outset, both were targeted for deployment in resource scarce settings in LMICs.

In both cases, funding for the development of a new product was not predicated on price, but instead on push funding, provided by a consortium of funders. The target end-product price of each product was set in a TPP from the beginning, at the lowest possible price to ensure long-term sustainable production. In neither case would commercial developers have developed a new product, given that the predicted economic returns were insufficient.



Implementing delinkage for antibiotics would require increases in upfront government funding to pay for pre-clinical and clinical drug development. It would also involve applying a mix of push and pull incentives tailored to the specific R&D activity and R&D actors involved.

A delinked financing model could be conducted fully within the public sector or in collaboration with not-for-profit actors such as GARDP. Some scholars have even suggested that a one-time investment of 1 billion USD to establish several non-profit R&D organizations would be the most sustainable long-term investment for antibiotic discovery and development.¹⁰⁴ In this model, R&D would likely be paid for exclusively through push funding, and the IP, which would either originate in the public sector or be created with public sector funding, would remain under public control.

In a delinked model, where pharmaceutical companies are involved in some or all parts of discovery, development, and production, the financing model should be designed to create sufficient public sector leverage over the antibiotic, no later than market entry. This way governments collectively design a global production and distribution system that enables both affordable access and stewardship. In practice, this could be done either through a public buy-out of the IP in the earlier stages (see Recommendation 3 starting next page) or by attaching conditions to funding which require that the IP is either managed by a non-profit product development partnership or licensed to a pooling mechanism, for example, the Medicines Patent Pool (see more under Challenge 4). By assigning the IP to a public-health driven product development partnership or pooling entity funders can ensure that the product is developed and brought to market with optimal and affordable access as a primary objective.

"We acknowledge the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development."

- UN Political Declaration on AMR, 2016.

3. Introduce targeted funding throughout clinical development

Even if significant cost reductions can be achieved by optimizing clinical trial processes and structures, the implementation of delinkage will require significant government funding via push funding. De-linkage may also require well-crafted pull incentives when the IP for a compound is owned by a private pharmaceutical company.

SMEs have generally supported the policy positions of the big multinational pharmaceutical companies in calling on governments to introduce substantial pull incentives in the form of MERs to support antibiotic R&D. Yet, SMEs and small biotech companies in Europe represented by the BEAM Alliance released a policy paper in November 2019, which also indicated support for other incentives more targeted toward the SME business model by making the point that:

"PULL incentives, as currently thought, mostly intends to reward the commercialization phase, but are unable to adequately reward the whole R&D value chain (biotech's and potentially their academic licensors) and attract investors for early-stage developments."¹⁰⁵

An assessment of the various pull incentives, in addition to the grants (push funding), which governments should consider in order to generate appropriate incentives for the actors involved in antibiotic R&D, is provided below.

Milestone prizes

Milestone prizes are a means to incentivize R&D through the promise of financial rewards upon achieving certain R&D objectives. As these prizes are paid out earlier in the development process, where private investments are smaller, milestone prizes offer far smaller rewards compared to billion-dollar MERs. Since they reward success, the risk to the funder is lower, and milestone prizes allow the funder to steer the direction of research by defining the conditions under which such prizes are paid out. Milestone prizes are also a useful incentive to link with end product profile attributes set out in TPPs (described above in Challenge 1).

A 2018 study, commissioned by the Swedish Public Health Agency¹⁰⁶ sought to identify which incentives were the most appropriate to support antibiotic R&D. It did so through qualitative interviews with member companies of the BEAM Alliance, as well as through extensive economic simulations of the expected impact of different incentives on various actors. It assessed the efficiency of three milestone prizes, one awarded at the end of the pre-clinical phase, one after phase I, and one after phase II, in a Monte Carlo simulation.¹⁰⁷ The study compared these prizes with the outcomes of two types of big pull incentives (a fully delinked and a partially delinked MER).

The study found that the amount required for milestone prizes would be between 24 million USD and 46 million USD. The simulation results also found that all three milestone prizes had better efficiency per approved antibiotic compared to either a fully or partially delinked MER. This makes milestone prizes a far more cost-efficient incentive option for governments to implement.

“Milestone prizes are a tool that acts with greater precision in the ‘financially most sensitive’ position in the pipeline and, accordingly, requires considerably lower amounts to achieve the same result as a MER...- According to the simulation results, they are also among the most effective incentives per market-launched antibiotic. Milestone prizes are also easy to test and particularly appreciated by SMEs. Finally...these incentives can be combined with grants to significantly increase their efficiency.”¹⁰⁸

Government buyouts of compounds

One mechanism that could provide an attractive exit option for smaller companies (that may not wish to shoulder the full burden of clinical development) is for one or a group of governments to acquire promising compounds. A public buyout of an investigational compound would enable investors and SMEs to recuperate their investments and generate a profit in a manner that mimics a big pharmaceutical companies' acquisition of promising compounds developed by smaller companies after phase I or phase II trials.

To avoid double payments by a government, these buyouts should account for the value of prior government funding for the development of the compound and compensate for public financing of R&D in the early, riskier phases. A government buyout could even be anticipated in advance and linked to early-stage push funding or milestone prizes awarded to a private developer. For example, a right of first refusal for a government to acquire an antibiotic could be conditioned through public funding.

One difficulty with a government buyout is that, if done unilaterally by one country, it could have adverse consequences. First, a government that has made a substantial investment through a buyout may not be willing to share it with other countries. Second, individual governments may each have different priorities; thus, antibiotics prioritized for buyouts by one or more HICs may be less appropriate or relevant for many LMICs. Third, there are no previous examples of governments acquiring promising pharmaceutical compounds through a government buyout; therefore, this is new territory. However, as the COVID-19 pandemic has illustrated, governments are willing to earmark billions of dollars to pay for and de-risk R&D, as well as make legal advance purchase commitments to buy vaccines and treatments once approved. Such upfront and back-end payments have essentially turned pharmaceutical companies into government sub-contractors (with the exception that pharmaceutical companies have been allowed to maintain full control of IP, despite billions of dollars of government and philanthropic funding).

Government buyouts may be more successful, equitable, and aligned with global public health needs if all countries (or multiple low, middle, and high-income countries) can pool financial resources and collectively negotiate and acquire antibiotics through a joint mechanism that can be provided sustainably and equitably to all people in need.

If done collectively through a pooled funding mechanism, government buyouts would offer the following advantages:

- Avoidance of unnecessary delays or cessation of development of a promising compound, in cases where companies with promising antibiotic compounds go bankrupt, decide to exit the field, or are bought out.
- Public control of intellectual property following a buyout, which facilitates easier application of a public health approach for both registration and distribution across countries.
- Governmental control over licensing the compound for needed follow-up research that generates data to guide the best clinical application of the drug; expanding indications for what the drug can be prescribed for; adapting the drug for vulnerable patient groups, such as pregnant women and children; and optimization studies on dosing and combinations of the drug with existing drugs.

4) Avoid “partial delinkage” to pay for research and development of new antibiotics

Even though delinkage may be both preferable and possible, it has not yet received the necessary support of key R&D funders and governments. Instead, the concept of “partial delinkage” has emerged through at least three different approaches. These approaches differ in the extent to which they “delinks” R&D costs from end product prices and sales volumes.

One approach, described and detailed by the EU-funded DRIVE-AB consortium, defines “partial delinkage” as a combination of an upfront lump sum payment (such as a MER) to companies, *in addition* to sales in commercial markets, subject to certain stewardship conditions.¹⁰⁹ Thereby only partly delinking payments from sales revenues.

A second approach to “partial delinkage” has been to implement full delinkage in some markets, for example, through collaboration with partners such as GARDP, while pursuing classic commercial sales strategies, with some commitments to respect stewardship and ensure access in what companies consider “commercial territories” (high-income countries and some middle-income countries).

The third approach has been to introduce reimbursement mechanisms. These are intended to augment the market (reimbursement) value of a new antibiotic through a subscription fee, or an additional top-up payment. At least five countries (France, Germany, Sweden, the U.K., and the U.S.) have either designed, piloted, or are considering reimbursement mechanisms.¹¹⁰

Each reimbursement mechanism that has been piloted, or that is under consideration, has been designed for a different purpose and is context specific. For example, Sweden’s pilot reimbursement mechanism intends to address the unavailability of certain antibiotics because the Swedish market is relatively small, in particular for antibiotics intended for multi-drug resistant bacteria, due to a relatively limited problem with these. To assure availability, the government is offering a guaranteed minimum income level to companies.¹¹¹ Since the primary purpose of Sweden’s reimbursement mechanism is to ensure availability, it is not designed to address stewardship concerns. Nor is it intended to stimulate innovation, as all antibiotics included in this pilot are already on the market – and the size of the guaranteed compensation is adjusted for this fact. In addition, this reimbursement model, if adopted in countries without similar stewardship practices and regulations as Sweden, could result in over-selling and misuse of the antibiotic.

“Partial delinkage” either:

- only partly delinks profit revenues from sales volumes

- delinks from both sales volumes and price, but only in some countries

- only delinks from sales volumes (and not price)

By comparison, the pilot reimbursement mechanism in the U.K., which applies a subscription model, will purchase new antibiotics through a multi-year contract for which the government provides an annual subscription fee of up to £10 million in exchange for as many doses as required.¹¹² This is designed to act as “an attractive pull mechanism for industry,” although to have the intended effect, it depends on “other countries to offer similar incentives in their own domestic markets, alongside regional or global market incentive solutions.”¹¹³ By switching from paying per drug unit to paying through subscription (which can be analogized to the business model employed by Netflix and Spotify), this model removes the commercial incentive for companies to maximize sales volumes before the drug goes off patent. It doesn't however ensure affordability (although payments do not exceed 10 million GBP per year per drug). In the U.K., the “subscription price” in the pilot has been negotiated, with the advice and assistance of the government's health technology assessment (HTA) agency NICE, which has calculated the reimbursement levels by applying a value-based approach.¹¹⁴

These reimbursement models may not be relevant or applicable in LMICs. This is because: (a) HTA agencies often do not exist, (b) governments may not have the financial resources to pay substantial “subscription fees” – even if such fees are modified to reflect a country's socio-economic classification, and (c) companies have demonstrated little to no interest in registering and marketing new antibiotics in LMIC markets.

As such, the reimbursement models currently being piloted in the U.K. and Sweden, and in other HICs, are national approaches and very context specific. Although such an approach may remove the link between R&D costs and the sales volumes in those specific contexts, it is highly questionable that such an approach would be appropriate, relevant, or workable in other contexts. This is especially true in LMICs that have very different constraints and challenges than HICs.

Although “partial delinkage” may appear to be a reasonable compromise to full delinkage, its application has several potentially negative consequences with respect to priority setting, stewardship, access, and developing appropriate formulations for neglected populations (See Box 6).

Box 6: Challenges with “Partial delinkage”

There are several concerns to be raised regarding “partial delinkage”:

1. If pharmaceutical companies are free to pursue higher revenues in HICs, as is the case with all three approaches described above, **it may negatively distort R&D prioritization** and sustain the current bias of antibiotic development toward the particular needs and priorities of the most profitable markets. This concern can be mitigated by creating a global R&D coordination entity and enforcing a global system of Target Product Profiles (TPP), as recommended for Challenge 1.
2. **“Partial delinkage” overestimates the strength of national stewardship policies in high-income countries.** HICs have a poor track record of overuse and misuse, with 50% of all prescriptions in OECD countries still estimated as being unnecessary.¹¹⁵ It would be irresponsible to establish a partially delinked model without dramatically improving stewardship policies and practices in all HICs.
3. A key element of a partially delinked model is that the intellectual property (IP) remains with the company. This means that the **developer retains the power to determine what follow-up R&D will be carried out** unless a government or philanthropic R&D funder has set out specific terms and enforceable conditions that require follow-up R&D. Companies may, of course, voluntarily enter into licensing agreements with other actors, for example, for the development of formulations for pediatric use, for pregnant women, or fixed dose combinations. However, unless such follow-up R&D is required as a condition of public funding or regulatory approval, such development priorities are left to the goodwill of the companies that hold the IP rights and may be ignored or unnecessarily delayed (as noted in Challenge 2).
4. **“Partial delinkage” can lead to a system of tiered pricing, with steep price differences between countries.** Such price discrimination can encourage drug companies to engage in predatory pricing practices in certain countries. For example, while prices of new Hepatitis C medicines in LMICs were as low as 50 USD per cure due to generic competition (permitted by patent holders or due to the absence of patent barriers), the price in HICs reached 94,500 USD per cure for the on-patent combination of Sofosbuvir and Ledipasvir, commercially known as Harvoni¹¹⁶ (such exorbitant prices would be unlikely for antibiotics). This price differentiation led the pharmaceutical company, Gilead Sciences, to introduce an anti-diversion policy in LMICs, which resulted in intrusive measures (to restrict sales and track patients) in low-income countries to assuage the company’s unfounded fear that low-cost drugs would be sold to people with Hepatitis C residing in HICs.¹¹⁷ In another example, two new antibiotics for TB – *Bedaquiline* and *Delamanid* – were steeply differentially priced, with high prices in HICs and somewhat lower, though still unaffordable, prices in LMICs.

New, on-patent antibiotics (beyond TB) are currently either not registered in LMICs or registered in very few such countries, thereby making the issue of pricing a moot point (see Challenge 4 for a full discussion on registration).¹¹⁸ According to the 2020 AMR Benchmark, at least six companies have explicitly backed using tiered pricing strategies, while eight other companies might also use tiered pricing strategies that take certain socio-economic factors into account.¹¹⁹

Challenge Four

Ensuring sustainable production, quality, procurement, and registration of novel antibiotics

Understanding the problem

Once a novel antibiotic has been brought through clinical development, there are several challenges with the current approach to global production, registration, and supply of antibiotics that need to be addressed.

Widespread shortages

Shortages of antibiotics are a chronic problem for many countries. This results in poor treatment options for patients and can be a driver of resistance when treatment providers are forced to prescribe alternative antibiotics. One example of an antibiotic in short supply is *benzathine penicillin G* (BPG) (See Box 7).

Box 7: Shortages of *benzathine penicillin G* (BPG)

BPG is used for treatment of rheumatic heart disease and is first-line therapy for syphilis. It is also the only treatment option currently able to prevent mother-to-child transmission of syphilis. According to a 2017 WHO survey, 39 countries out of 95 surveyed reported a shortage of BPG. In 10 countries this led to switching to less effective alternative treatments (*Ceftriaxone*, *Amoxicillin*, and *Erythromycin*) unable to prevent mother-to-child transmission.

The reasons for the BPG shortages include¹²⁰:

- A price cap placed on the medicine in some countries may have kept the price too low, especially since it is an injectable drug that requires a significant financial investment for its manufacture.
- Quality of manufacturing, as of 2017, was a challenge, with none of the three API manufacturers having market authorization from a stringent regulatory authority, and with two of those manufacturers having had to interrupt production due to quality concerns.
- Furthermore, minimum purchase quantities from several countries was often not enough to meet minimum production requirements from manufacturers.

Several reasons on both the supply and the demand side contribute to antibiotic shortages arising. On the supply side, the current global supply chain is fragile and relies on only a few manufacturers based in a few countries. For some antibiotics, there are just one or two major manufacturers of the active pharmaceutical ingredient (API) supplying global production; therefore, disruptions can lead to global stockouts and shortages.¹²¹ A lack of transparency in the global supply chains makes it difficult to assess the full extent of the current system's fragility.

A number of countries are taking national steps to address shortages. For example, in July 2020, the government of India decided to incentivize the local production of 53 medicines, including several antibiotics, key starting materials, and APIs, in order to avoid future supply disruptions of key medicines.¹²² Similarly, the European Union is considering reshoring API production for essential drugs, including antibiotics, to Europe.¹²³

On the demand side, fragmented and unpredictable demand forecasting and procurement are problems in many countries, especially where these functions are decentralized. Such fragmentation of demand and of procurement can limit a country's ability to secure adequate supply.

Poor production practices

Antibiotic discharge from manufacturing facilities is a result of inadequate production standards and waste removal at sites for raw materials and API manufacturing of antibiotics. Such discharge is a driver of resistance development in the environment. The majority of the production of raw materials and APIs is based in China, while an estimated 40% of the manufacturing of the finished product is based in India.¹²⁴ High concentrations of antibiotics have been found in the local water bodies surrounding pharmaceutical production clusters in several states in India.¹²⁵ Moreover, a 2016 study of 34 manufacturing sites found 16 sites to be harboring bacteria resistant to antibiotics.¹²⁶

Strengthening regulations and restricting the use of raw materials and API could reduce contamination but should not be done in a way that jeopardizes the availability or the affordability of antibiotics. In 2018, the pharmaceutical industry launched an initiative to self-regulate antibiotic discharge through the AMR Industry Alliance. This initiative,

however, has not included the views of many of the smaller manufacturers based in LMICs. Although these smaller manufacturers similarly need to improve production practices, they may face financial and technological challenges in adapting to new rules and regulations that were designed by and for large companies within the AMR Industry Alliance. This matter since smaller manufacturers can play a critical role in ensuring availability of essential health products in LMICs that are otherwise ignored by larger pharmaceutical companies. Additionally, despite having developed standards for discharge limitation, none of the big companies selling antibiotics have so far been willing to publish results from audits of their production plants or from their subcontractors.¹²⁷ A broader approach than what has been developed in the AMR Industry Alliance is needed in order to also address adaptability challenges for smaller manufacturers as well as enforceability of standards and effective accountability measures.

Lack of Registration

After the first regulatory approval in HICs, registration of new antibiotics in other countries is often delayed and sometimes ignored. Of the novel antibiotics entering the global pharmaceutical market between 1999 and 2014, only 12

out of 21 products were registered in more than 10 countries,¹²⁸ and those registrations were concentrated in HICs.¹²⁹ For antibiotics introduced since 2014, registrations have been filed in fewer than five countries per year, slowing down approval and use.¹³⁰ The Access to Medicines Foundation's AMR Benchmark from 2020 also found that older off-patent products are still unlikely to be widely available. So-called "forgotten antibiotics" – old, but still clinically useful antibiotics – were found to be largely unavailable in LMICs.

Poor quality

Poor quality antibiotics are a serious problem. A review of 100 scientific articles, conducted by the WHO, found that approximately 10% of all medicines sold in LMICs are substandard or falsified.¹³¹ The study estimated that up to 72,000 deaths from childhood pneumonia are attributable to poor quality antibiotics. More generally, according to the WHO Global Surveillance and Monitoring System, 17% of the reports to the Monitoring System of falsified or substandard medicines were for antibiotics, and 20% for antimalarials, making antimicrobial drugs the largest category of falsified and substandard medicines.¹³² More analysis in this field is required, but it is beyond the scope of this report.

Recommendations.

Many of the challenges within the antibiotic market, such as shortages, delays with registration, and quality assurance, are transnational and even global problems. These challenges would benefit from being addressed globally through a system of global rules-based governance under the aegis of the WHO alone or with other relevant multilateral UN agencies.

An example of global rules-based governance is the Global Development and Stewardship Framework, mandated by member states at the 68th World Health Assembly in 2015 and recalled in the UN Political Declaration on AMR in 2016. The implementation of this framework could facilitate development, stewardship, and access to new and existing antibiotics under the guidance of the WHO and the other Tripartite agencies. Unfortunately, progress has largely stalled due to political apathy from governments and a general unwillingness to submit to an international framework involving international adherence and cooperation.

The following sections will first make recommendations on what governments should aim to achieve through global governance in the field of antibiotic R&D. Recommendations are then presented on how governments in the interim, can start to address the problems, either alone or in collaboration with several other governments.

The COVID-19 pandemic has exposed the boundaries of current global health cooperation. Rules-based global governance can introduce common rules, priorities and binding commitments.

Recommendations based upon global governance

Rules-based global governance of manufacturing, quality, registration, supply, and procurement of antibiotics could alleviate several of the problems mentioned previously. Assuming that such a framework is put in place, it should work to achieve the following:

1. Address imbalances between supply and demand through pooled procurement

Global governance could help address imbalances between supply and demand, which result in antibiotic shortages. There are several measures that governments can jointly execute to expand the supply of critical antibiotics, including:

- Providing financial incentives or subsidies to manufacturers that encourage adequate production, including production of low-margin antibiotics.
- Mandating transparency in the supply chain.
- Encouraging a diverse manufacturer base of both active pharmaceutical ingredients (API production) and the end product through multi-source procurement.
- Improving predictability and reliability of demand and forecasting at the global, regional, and national level, and communicating this to the manufacturers.

One mechanism with the potential to address most of the above points is pooled procurement. Whether it is developed as a global entity or set of regional entities, pooled procurement can improve affordability and provide predictability for suppliers by improving demand forecasting. Depending on the design and mandate, a pooled procurement entity could even help ensure timely distribution, manage anticipated or sudden disruptions of supply or demand, identify and assist new suppliers when necessary to meet increased demand, or replace a supplier that is exiting the market. A pooled procurement entity could also restrict procurement to those suppliers who are either producing through an internationally established licensing mechanism, abiding by specific manufacturing regulations, or meeting other regulatory requirements for older antibiotics. This could also facilitate collective action to implement environmental standards for production.

There are longstanding precedents for establishing both global and regional pooled procurement. Established in 2001, The Global Drug Facility for Tuberculosis (GDF)¹³³, grew out of a declaration made a year earlier by countries attending the Ministerial Conference on TB and Sustainable Development in Amsterdam to “build new international approaches towards ensuring universal access to, and efficient national systems of procurement and distribution of anti-TB drugs”.¹³⁴ Today, 20 years later, the GDF has been able to establish a stable supply of quality-assured antibiotics and diagnostics to address TB on behalf of 142 countries. Similarly, the PAHO Revolving Fund pools procurement of vaccines and related products for 41 countries in the Latin American region and was established all the way back in 1977.¹³⁵

One challenge, however, with pooled procurement is that procurement rules and tendering procedures can disincentivize having several manufacturers, especially for drugs for which there is little or irregular demand. If one company has a cost advantage or can accept lower margins for the product, this can lead to other manufacturers exiting the market, thereby increasing the risk of supply disruptions in the long-term. This issue could be addressed by procurement guidelines that select several “winning” suppliers.

Another challenge with pooled procurement is the multiplicity of national laws, which legislate the procurement of medicines through government tenders only. However, there are examples of countries setting up exemptions for specific medicines, such as for medicines to treat and prevent tuberculosis or HIV.¹³⁶

Pooling procurement to overcome issues of lack of access, high prices, shortages and stock-outs is a long-standing practice.

2. Controlled production and supply

Global governance could facilitate the worldwide management of patents and other intellectual property for novel antibiotics. If public funders, for example, required intellectual property for novel antibiotics to be collectively managed through a global patent pool, production licenses could be issued by the patent pool to an appropriate number of manufacturers. These would then be required to abide by clearly defined terms and conditions related to manufacturing, production, quality, distribution, and marketing.

Widespread and unregulated production and distribution of new antibiotics could be avoided by limiting production to a specified number of international suppliers and introducing measures to prohibit or stop production from unauthorized manufacturers. The Medicines Patent Pool (MPP), which manages a patent pool to expand supply on behalf of LMICs for medicines to treat or prevent HIV and AIDS, Hepatitis C, and TB, has also studied the feasibility of licensing new antibiotics. The MPP noted in a study that “rather than broadly licensing to multiple manufacturers to promote wide availability and generic competition, the MPP would need to limit the number of licensees to ensure that the products are made affordably available to those who need them while preventing overuse.”¹³⁷

Well-designed global governance rules would also facilitate appropriate long-term management of antibiotics, which stretches beyond the expiry of the patent term. It would also address the fact that most novel antibiotics will not have patent protection in *all countries*, even when such products first enter the market.

Such global governance rules are not unprecedented. Mechanisms have been put in place for controlled medicines (e.g., narcotics), for which a series of international agreements now govern and restrict all aspects of the supply, production, export, marketing, and distribution of such products. While probably effective in reducing irrational use, this highly controlled approach has also led to severe access problems for opioids and pain relief. As such, this model goes too far in restricting access to be compatible with the need to ensure access to lifesaving antibiotics¹³⁸ that compared to controlled medicines, have a larger spectrum of indications, and are used in multiple and diverse contexts. However, the rules and the enforcement of such rules for controlled substances illustrate that such global frameworks for drug management can be negotiated and implemented.

3. Promote environmentally appropriate antibiotic production

Global governance could establish international standards that guide and regulate the production of antibiotics to discourage or prohibit environmentally damaging practices. Such regulation could be even be enforced and accomplished through procurement requirements and/or through preferential procurement of appropriate end products. This could be coupled with subsidies and incentives for implementing environmentally appropriate practices.

For smaller manufacturers, in particular, which may have neither the financial capacity nor the technology to adjust to such requirements, an international system or fund that would subsidize adjustments and provide access to technology and know-how should be considered. Especially if such producers are committed to manufacturing quality-assured antibiotics needed in LMICs.

4. Facilitate timely registration

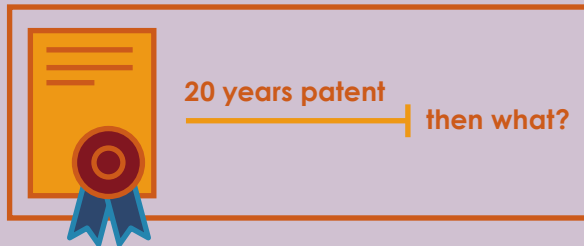
Over the last two decades, the WHO has invested significant resources to facilitate the timely registration of quality branded and generic medicines in LMICs. Funders of R&D should ensure that the WHO Prequalification (PQ) Program and the Collaborative Registration Procedure (CRP) are made available to all developers and follow-on manufacturers for approval of new antibiotics, and require that product developers pursue this regulatory pathway for LMICs to facilitate timely and widespread registration.

At present, the Collaboration Registration Procedure includes 58 countries, and its membership is growing. The CRP accelerates registration through two mechanisms. First, for those products which have been pre-qualified by the WHO through its PQ Program, it improves information sharing between the program and national medicines regulatory authorities. That way, national authorities can utilize the outcomes of the PQ Program, thus eliminating duplication of work and speeding up regulatory approval. Second, the WHO maintains a CRP for medicines already approved by a stringent regulatory authority.¹³⁹ An applicant, with the agreement of a stringent regulatory authority that has approved a product, will share the full assessment and inspection reports for the product in question with participating national medicines regulatory authorities. The national medicines authorities will use the data to support their decision-making regarding registration and seek to issue a decision within 90 days.

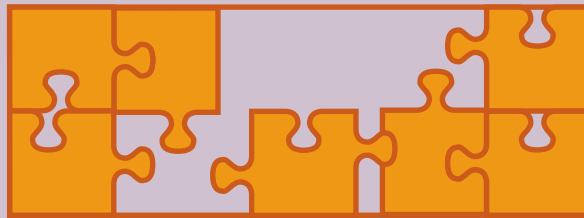
Regional registration schemes could also enable low-resource countries to pool resources, share responsibility for assuring quality, and avoid duplication of efforts. One critical development has been the creation of the African Medicines Agency (AMA). Upon ratification, the specialized African Union institution will become the continent's regulatory body mandated to provide leadership through coordination and harmonization of strengthened national medicines regulatory bodies via the different Regional Economic Communities.

Sustainable management of antibiotics

Current approach:

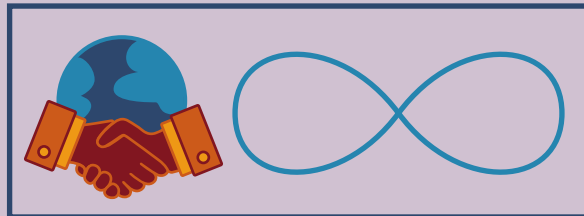


Patent-based system
Patent protection offers a time-limited means of control.



Uncoordinated national action
National solutions will be inadequate as a means to facilitate appropriate long-term management of antibiotics.

Needed approach:



Global rules-based governance
Well-designed global governance rules on responsible management of antibiotics on an end-to-end basis can overcome problems with fragmentation and durability constraints of the current system.

Recommendations to take forward even in the absence of global governance

The absence of a global governance framework should not discourage governments from acting. In the interim, there are several measures that governments can collectively or individually introduce to improve sustainable access, registration, and manufacturing of antibiotics. An incremental approach should however create a pathway to facilitate, or at least not hinder, an eventual global framework.

1. Government(s) should adopt national legislation that sets antibiotic production standards

Governments can manage and regulate the production of antibiotics and APIs. In January 2020, the Government of India published a draft bill to limit the level of antibiotic residue that can be released into the environment. This would allow for new rules that would apply to all drug manufacturing companies in India for 121 common antibiotics.¹⁴⁰ While some have applauded the legislation, there are concerns that it may be difficult to enforce.¹⁴¹

Non-producing countries can work to ensure that rules on Good Manufacturing Practice (GMP) include environmental obligations – an approach the WHO also is examining.¹⁴² As noted in previous paragraphs, placing additional demands on producers should be carefully balanced with the need to protect affordable access to antibiotics to avoid the costs being passed onto patients, especially for patients paying out-of-pocket. Appropriate technology transfer to support such adaptation of production capacity would be important to couple with increased requirements.¹⁴³

2. Government(s) should set procurement rules and/or guidelines that encourage environmentally appropriate production

One or more governments can create procurement rules for antibiotics that improve transparency and discourage improper practices throughout the supply chain. To the extent that “polluting” production activities have been outsourced to LMICs, where production is less expensive, it is insufficient to simply penalize manufacturers in those countries for not abiding by HIC standards. Instead the burden of meeting environmental standards should be shared. Norway, for example, has launched a new antibiotic procurement policy in which suppliers that can document satisfactory environmental practices will have an “advantage” during the selection tendering process (environmentally friendly production weighted by 30 percent).¹⁴⁴ Sweden, having updated its sustainability criteria, has introduced contract clauses in its procurement policy that require suppliers to have procedures in place to map and prevent emissions.¹⁴⁵ Short of globally mandated standards, the best way forward would be for a regional governance body, such as the European Union, to introduce common guidelines.

3. Government(s) should require patent pooling as a condition on public funding

Patent pooling, as discussed previously, is one means to manage the IP created in the public and private sector and to manage the development of a promising compound. In the absence of a global agreement to manage IP, several governments could cooperate to ensure the licensing of IP to a patent pool (such as the Medicines Patent Pool), on the understanding that sub-licenses could enlist several manufacturers that would be legally bound by agreed standards that promote responsible use and affordability.

For such patent pooling arrangements to be effective however, participation would need to be required as a condition of public funding (as described under Challenge 3). Such funding requirements would enable a patent pool to expand the territory of a license agreement through larger payments or incentives (i.e. developers forego their exclusive rights in a specified territory in exchange for a financial payment). Challenge 3 identified several such reward or financing mechanisms that could be combined with licensing, including push funding, milestone prizes, and government buyouts of IP. Without pairing licensing and funding together, the pooling negotiations will have to rely on voluntary corporate social responsibility, which is unlikely to be as effective.

IP pooling can also be used to promote the responsible introduction and management of antibiotics in countries. Although this would not ensure that all countries (and all manufacturers) abide by one international approach, informal pressure on countries and manufacturers that do not follow international best practices, coupled with strengthened health systems (see challenge 5), could help curtail inappropriate use.

For patent pooling mechanisms to be effective, participation should be required as a condition of receiving public funding.

4. Governments should support public and/or not-for-profit production

For decades, governments have abandoned public and national production of medical products, opting instead to allow the development of international supply chains around the world, with production concentrated in a few countries such as China, India, South Korea and Italy.

However, the merits of public production deserve more focus as one approach to the manufacturing of medical products of special public health importance. In its announcement of a new "European Health Union," the European Commission suggested the new EU Health Emergency Preparedness and Response Authority (HERA) could engage in public production.¹⁴⁶ In September 2020, California's state government (on its own, California is the world's fifth largest economy) enacted a new law to permit the State to produce its own generic medicines (which would be accomplished through outsourcing production to a private manufacturer, but with the government retaining control of supply and distribution).¹⁴⁷ These emerging efforts join several governments that never abandoned public production (for example Brazil and Thailand).

This momentum is also seen in the U.S. Government's announcement of its intention to support a new national manufacturer for generic medicines, the Phlow Corporation. This entity is intending to work with private manufacturers to produce APIs and finished pharmaceutical products for essential medicines, including several essential antibiotics.¹⁴⁸ In addition, senior U.S. lawmakers have introduced legislation, such as the Affordable Drug Manufacturing Act,¹⁴⁹ which would commit the United States to establish an Office of Drug Manufacturing to manufacture select generic medicines and offer those to consumers at a fair price.

The merits of public procurement or not-for-profit production deserve more focus as one approach to the manufacturing of medical products of special public health importance.

Public production of essential antibiotics allows governments to address several problems, such as shortages (including API production), environmental pollution, and lack of registration. Public production also facilitates public control over the formulation of access and stewardship policies, as well as the procedures to introduce and distribute novel antibiotics.

Nevertheless, public production can have its challenges in countries where doctors earn part of their salaries from sales of medicines. Uptake of public sector manufactured antibiotics can be insufficient, as lower margins are applied for prescribing publicly-produced medicines compared to sales of privately manufactured antibiotics. While lower margins reduce the cost of the medicine for the patient, they also reduce income for hospitals and general practitioners. In these settings, measures need to be introduced that completely separate brand selection from the income of prescribers. More generally, misaligned incentives that drive unnecessary use and as a result, resistance, need to be addressed in all contexts and forms by governments.

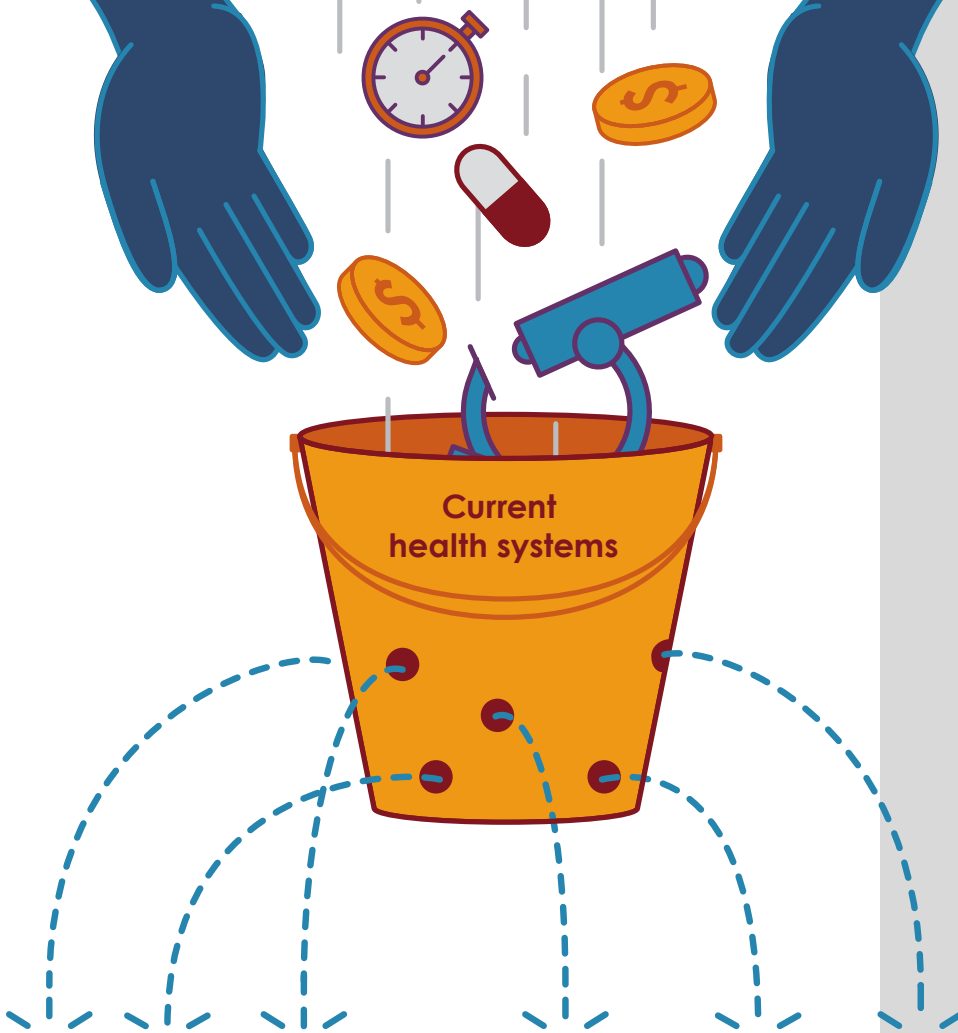
Public production to assure the affordability and availability of antibiotics of public health importance would be easier to achieve if governments worked together to invest in the production of API. Production itself could be done through existing contract manufacturing organizations, which are already widely used by pharmaceutical companies for their own product lines. Such coordinated efforts have already worked on a smaller scale within the private health system in the United States. Civica Rx, a not-for-profit pharmaceutical manufacturer backed by several U.S. hospital systems, was launched in 2018 with the aim of overcoming chronic drug shortages. Civica Rx now produces and supplies essential generic medicines, including several antibiotics, to 1,200 hospitals in the United States.¹⁵⁰

Misaligned incentives that drive unnecessary use and as a result, resistance, need to be addressed in all contexts and forms by governments.



Challenge Five

Ensuring sustainable access to new antibiotics in countries



Understanding the problem

Simultaneously expanding appropriate access to antibiotics, while restricting inappropriate use of all, and in particular, new antibiotics, is a unique challenge in global health. Much more focus should be placed on how new antibiotics can be responsibly introduced into health systems in both HIC and LMICs without repeating the historical mistakes of overuse and misuse of antibiotics, and lack of access.

Misuse and overuse of existing antibiotics is widespread in all countries. According to the U.S. CDC, 1 in 3 antibiotic prescriptions are unnecessary in the U.S., equaling 47 million excess antibiotic treatment courses every year.¹⁵¹ The OECD has estimated that roughly 50% of the prescriptions for antibiotics in the OECD countries are unnecessary.¹⁵²

In LMICs, where health systems are often weak and underfinanced, overuse and misuse of antibiotics can be widespread. Yet at the same time, these countries often also struggle with lack of access to essential medicines, including effective antibiotics. Unaffordable prices for med-

icines are still a significant barrier to access for many, with up to 90% of the population in low-income countries paying for their medicines out-of-pocket.¹⁵³

Antibiotic use in LMICs has been increasing in recent years, after low levels of consumption historically. For example, a 2014 study found that the BRICS countries (Brazil, Russia, India, China, and South Africa) accounted for three-quarters of the global increase in antibiotic consumption between 2000 and 2010, even though the increase in population in these countries was only one-third of the total population growth over that same period.¹⁵⁴ Nevertheless, even with steep increases in the consumption of antibiotics in these countries, the per capita consumption in LMICs remains well below that of HICs. Between 2000 and 2010, the U.S. per capita consumption of antibiotics was twice as high as in India and three times as high as in China.¹⁵⁵

HICs consume more than two times the doses of low-income countries, measured in DDDs per 1,000 inhabitants per day. This is unreasonable since the burden of infectious

diseases is far higher in LMICs. HICs, having both financial resources and well-developed health systems in place, have a moral responsibility to urgently reduce their excess use.

Antibiotic consumption in HICs has been relatively stable since the year 2000, as depicted in figure 6. Even if increases in global consumption are mainly due to higher consumption in LMICs,¹⁵⁶ it is likely that part of this increase is linked to increased access to healthcare and thus appropriate use of antibiotics.¹⁵⁷

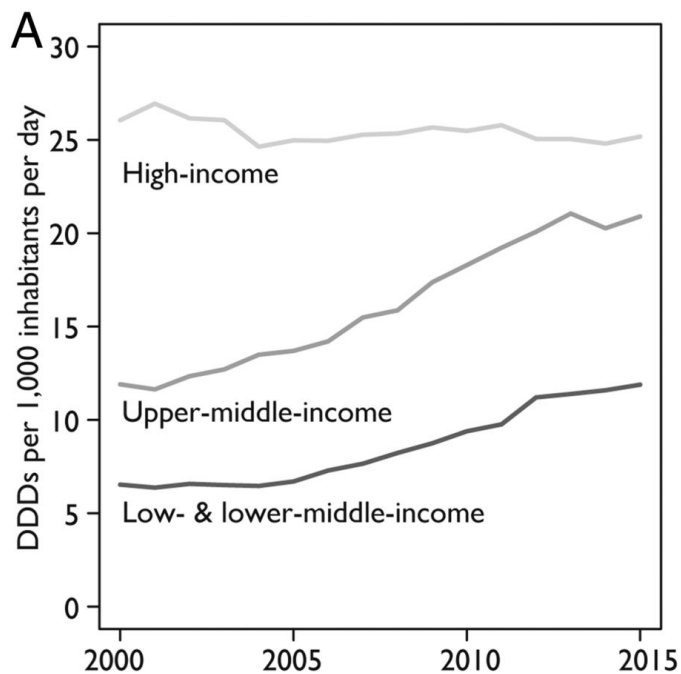


Figure 6. Growth in global antibiotic consumption is mostly driven by use in LMICs. The figure was first published as Fig. 2A in Klein, E. et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Nat Acad Sci* 115(15):E3463-E3470 (2018). <https://www.pnas.org/content/115/15/E3463>

As antibiotic resistance develops and spreads, the cost of alternative antibiotic treatment that can overcome such resistance, e.g., second- and third-line antibiotics, increases. A study from India suggested that the median overall additional cost to treat a resistant bacterial infection is 700 USD, which is equivalent to 442 days of work pay for the average rural male worker.¹⁵⁸ Lack of affordable access

to antibiotics, whether driven by high prices, by lack of availability and registration of the drug, user fees, or other expenses that discourage people from visiting a doctor, is also a driver of antibiotic resistance. Individuals may self-medicate with antibiotics sold over the counter without prescription at the pharmacy or in the informal market. For some, self-medication can be the only affordable health care option compared to visiting the doctor or going to a hospital. For the nearly two billion people that live on less than 3.20 US Dollars (USD) per day,¹⁵⁹ and with poverty on the rise again due to the economic fall-out of the COVID-19 pandemic,¹⁶⁰ the lack of access to effective antibiotics will remain one of the most pressing challenges and a cause of avoidable morbidity and mortality.

Moreover, all countries have a responsibility to address both the underlying and the external drivers of inappropriate use. One example of such a driver is the practice of prescribers earning parts of their income from prescribing certain drugs as described in Challenge 4. Another is the practice within pharmaceutical companies of providing sales-based bonuses to sales staff. The AMR Benchmark report from 2020 found that just six out of 22 companies surveyed in the report have actually removed such damaging bonuses by themselves. One company has even backtracked from previous commitments by reintroducing these bonuses.¹⁶¹ There is overwhelming evidence that exposure to pharmaceutical companies' promotional activities has a negative impact on prescribers' practices (such as more expensive or less appropriate prescribing).^{162,163,164}

Inappropriate use of antibiotics can be a challenge even in countries with affordable and universal healthcare coverage and a well-developed health care system. In Thailand, a country of 70 million people, a 2018 study found that licensed antibiotic distribution involved over 700 importers and about 24,000 distributors, e.g., retail pharmacies and wholesalers.¹⁶⁵ It also found that most antibiotics could be bought from pharmacies without a prescription and that there were no restrictions on the quantities of antibiotics that could be sold to any individual. The introduction and distribution of new antibiotics into such settings is very complex, and even more difficult in countries with less developed healthcare systems and health infrastructure than Thailand.

Recommendations.

National governments are responsible for the introduction and distribution of a new antibiotic in a way that guarantees its safe and responsible use, assures equitable access, and minimizes the risk of the emergence of resistance development. However, preserving the effectiveness of both new and old antibiotics is also a global collective responsibility. Worldwide mismanagement of antibiotics demonstrates that individual developers should not decide how patients can secure access to new antibiotics. A product by product, company by company approach will not work. Instead, governments must actively intervene throughout the development process so that new antibiotics are managed effectively.

Strengthening healthcare systems globally and providing financing options for LMICs

Antibiotic resistance cannot be eradicated – it can only be managed. Effectively addressing antibiotic resistance is intrinsically linked to well-functioning, sufficiently financed, and well-staffed national healthcare systems. In the wake of the COVID-19 pandemic, and before any novel antibiotic class is approved, governments have up to a decade to strengthen healthcare systems worldwide, which is consistent with the global commitment to achieve universal health coverage by 2030, set out in the Sustainable Developmental Goals (SDGs).

Global efforts to contain antibiotic resistance will only be as strong as the weakest healthcare systems (and food-productions systems, which are outside the scope of this report). For such system strengthening to take place in LMICs, financing options must be available. This requires urgent global financial mobilization and must be part of the global discussions on establishing financial incentives to fix the broken innovation model for antibiotics. Without investing in the healthcare systems that ultimately bear the responsibility of handling new antibiotics prudently, any efforts made to fix the collapsed R&D system will be in vain.¹⁶⁶

Without investing in the healthcare systems that eventually are supposed to manage new antibiotics, efforts to fix the collapsed R&D system will be in vain.

Support civil society efforts to develop human resource capacity and structures

Antibiotic resistance does also not yet have strong, dedicated set of civil society actors and organisations as seen for other diseases and global health issues. CSO actors could have partnered with Ministries of Health and providers, clinics and hospitals within healthcare systems to introduce new treatments (as was seen early on in the HIV epidemic and for TB). Governments should prioritize supporting civil society in building a bottom-up approach to developing human resource capacity and structures, as well as increasing awareness of the causes and consequences of antibiotic resistance.

In Sweden, the Strategic Group for Rational Antibiotic Use and Reduced Antibiotic Resistance (the Strama Network) could serve as inspiration for a bottom-up approach within professional ecosystems in other countries. The Strama Network was first established as an informal group of concerned infectious disease doctors but, since its formal creation in 1995, it has grown to include representation from infectious disease societies, local and national authorities, and broad range of other relevant stakeholders. Strama has become an important actor in shaping and innovating national antibiotic stewardship policies and clinical practice, and the model has proven very sustainable. A relatively high level of awareness, participation, and commitment to addressing antibiotic resistance in wider Swedish society today is a positive spillover of Strama's efforts.¹⁶⁷ Applying this approach would obviously need some adaptation to account for different contexts and/or professions in other countries.

Civil society are indispensable actors in developing human resource capacity, anchoring practice and structures, as well as increasing awareness about antibiotic resistance.

Establish a global Taskforce for the introduction of novel antibiotics

Valuable lessons can be learned from the field of tuberculosis. New antibiotics were approved nearly a decade ago, after a 50-year innovation standstill. In 2013, the WHO convened a group of experts to form a “Task Force for New Drug Policy Development,” financed by the Bill and Melinda Gates Foundation, to discuss how these new TB drugs should be responsibly introduced. Initially, the Task Force convened consultations with drug developers to identify and address barriers as early as possible, in order to develop a responsible, public health centered, drug introduction and distribution model. The expert group's efforts ended when funding was stopped after one year. The work of the expert group was then condensed into a policy document called the “Policy Implementation Package”,¹⁶⁸ which contains six key elements:

1. **Minimum requirements for country preparedness and planning.** Developing minimum requirements for the health and regulatory environment, laboratory capacity, drug procurement systems, case management, monitoring and evaluation, pharmacovigilance, financial resources, and country support.
2. **A National Implementation Plan for introduction.** This should outline the operational models for the introduction of new drugs or regimens, depending on the prevalence of the disease, the level of preparedness, and the drug or regimen to be introduced.
3. **Monitoring and evaluation of new drugs and regimens,** including pharmacovigilance to monitor safety (particularly if the drugs are introduced following conditional regulatory approval) as well as drug resistance surveillance .
4. **Private sector engagement.** Countries should develop a plan for how private sector healthcare should be involved in the introduction of new drugs.
5. **A systems approach for ensuring uninterrupted supply of quality-assured drugs.** This requires countries to develop a clearly established national procurement and supply chain management system to ensure an steady supply of new medicines.
6. **Operational research.** This can help to evaluate the public health impact, measure feasibility, cost effectiveness and acceptability, to assist countries in the implementation process and adjustment of scale-up processes.

All these elements are relevant for the introduction of novel antibiotics and clearly illustrate why increased global efforts and collaboration to strengthen existing health systems in all countries are important. However, antibiotic resistance is also profoundly different from TB. For example, antibiotic resistance is not a disease in itself and does not have a well-established vertical disease program structures at the WHO and in countries for treatment and surveillance. It also does not make sense to establish new vertical approaches, as this would require multiple vertical programs for a number of indications e.g., sepsis, UTIs, pneumonia, gonorrhea, which are just some of the many diseases and conditions for which access to effective antibiotic is essential.

A new global task force, with a scope and mandate that resembles the former WHO Task Force for New Drug Policy Development, could develop recommendations to guide countries' introduction of novel antibiotics and identify gaps and financing needs towards this end. This would establish a platform for structured and transparent conversations with developers, manufacturers, regulatory agencies, and funders on how to adapt existing practices as early as possible to successfully introduce new antibiotics into countries. A project under development between GARDP, the WHO, Unicef and The Clinton Health Access Initiative (CHAI) called SECURE is in fact going some of this way in trying to develop a pilot model for introduction of new and old antibiotics into countries.

The work of such a global task force should be designed based on the input and perspective of LMICs and civil society, which is why appropriate global representation is crucial. It should work transparently and with strict conflict-of-interest rules in place. Ideally, the task force should be an integrated part of a permanent global antibiotic R&D coordinating entity, as recommended under Challenge 1 to ensure that an end-to-end approach is applied to achieve end goals for access and stewardship in all countries.

Final remarks.

Antimicrobial resistance is a growing global health crisis.

Its impacts are already being felt around the world, especially in LMICs, which lack the financial, human, and health-care systems resources to surveil and reduce the spread of resistant bacteria.

Too often, proposed policy solutions to the crisis in antibiotic development have focused solely on fixing the business model for antibiotics by trying to make antibiotics as profitable as other therapeutic areas. This approach ignores the broader discussions about the access problems associated with excessive drug pricing in many countries and places too much emphasis on just one problem in an overall broken model.

As this report argues, the goal should not be to narrowly focus on fixing the antibiotics business model for pharmaceutical companies – governments should use the opportunity to create a sustainable end-to-end solution that more ambitiously seeks to ensure sustainable access to effective antibiotics for all. Collective planning by governments has gained momentum over the last decade with the agreement by health ministries to the 2015 WHO Global Action Plan and, in 2016, by the Heads of State to the UN High

Level Political Declaration on Antimicrobial Resistance. The recent announcement of the One Health Global Leaders Group (GLG) on Antimicrobial Resistance is also a welcome step. It has the potential, as ReAct stated in an open letter to the newly announced co-Chairs in November 2020,¹⁶⁹ to provide leadership that would elevate antimicrobial resistance to the highest level of the global health and development agenda, mobilize resources, promote global collaboration, and hold governments and other actors accountable.

Leadership and coordination are urgently needed. Several challenges and recommendations in this report have been partially addressed by individual governments, companies (or groups of companies), foundations, and international health agencies. Yet, these efforts reflect the narrow perspectives and contexts of single countries, companies, or foundations, and either fall short of the scale of what is required, or do not account for the needs of populations, healthcare systems, and governments in LMICs.

International cooperation between governments is difficult to achieve, even when governments can work with and trust one another. Today, growing competition and mistrust

between governments undermine collective action. We believe that there can only be sustainable progress against antibiotic resistance if governments collectively set rules, define priorities, provide sustained funding, and enforce agreements. The slow pace of collective rule-making and negotiation in the near-term may create an impression of insufficient global progress, but such efforts will pay dividends in the long-term, especially since antibiotic resistance requires decades of persistent, flexible, and ongoing cooperation to address an evolving problem.

The COVID-19 pandemic illustrates how governments, scientists, and some non-state actors can work together to address a common challenge. During this pandemic, scientists and research institutions have worked more promptly, transparently, and openly to share knowledge, data, and scientific information. Through efforts of some governments and global health agencies, two separate facilities, the Access to COVID-19 Tools Accelerator (ACT-A) and the COVAX Facility, have been established to identify, develop, distribute, and/or purchase medicines, vaccines, and diagnostics to assist national efforts to control the pandemic. The COVAX Facility now includes 184 countries, although there are significant concerns with the Facility's governance, transparency, approach to pricing, and allocation of supply, which must be addressed.

The COVID-19 pandemic has also exposed the boundaries of global health cooperation. Only an estimated 10% of the funding pledged to the ACT-A has been provided at the time of writing this report. Many governments, even though they have nominally supported the development and sharing of new technologies to combat COVID-19, have practiced so-called "health technology nationalism" – prioritizing their own needs first and reserving "first-in-line" access to any vaccine or medicine that may emerge. Pharmaceutical companies, despite having received billions of dollars of government funding that reduces risk from the entire R&D process, as well as government guarantees to purchase new medicines and vaccines, have refused to pool their intellectual property, or (with few exceptions) expand supply of medicines or treatments through licensing and technology transfer agreements even when demand outgrew supply capacity. The new vaccines are already translating into blockbuster revenues for companies and their shareholders, while failed candidates may end up having

little to no financial impact on an unsuccessful company. For those who wish to find a sustainable and equitable path forward to address antibiotic resistance, the COVID-19 pandemic is a reminder that, for all the high-minded rhetoric, promises, and aspirations of governments and companies, the reality often falls far short of the mark.

This report has been focused on identifying pragmatic solutions to respond to the dearth of new antibiotics to address antimicrobial resistance. In particular, it sets out the end goals and identifies the five main challenges that must be tackled with these goals in mind in order to solve the global crisis in antibiotic R&D. We believe the recommendations are more likely to be supported and successful if governments cooperate and work together through a system of rules-based global governance to introduce common rules and priorities and focus on what is needed for public health. We also believe that such policies will only have a public health impact if those who hold power, whether it is governments, foundations, funders, or companies, are committed to promoting solidarity, achieving equity, and ensuring sustainable access to effective antibiotics for everyone, everywhere.

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